UNIVERSIDADE DE SOROCABA

PRÓ-REITORIA DE PÓS-GRADUAÇÃO, PESQUISA, EXTENSÃO E INOVAÇÃO

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS FARMACÊUTICAS

Izabela Fulone

AÇÕES E ESTRATÉGIAS PARA O ACOMPANHAMENTO DE PACIENTES COM TRANSTORNOS MENTAIS DESINSTITUCIONALIZADOS

Sorocaba/SP

2020

Izabela Fulone

AÇÕES E ESTRATÉGIAS PARA O ACOMPANHAMENTO DE PACIENTES COM TRANSTORNOS MENTAIS DESINSTITUCIONALIZADOS

Tese apresentada à Banca Examinadora do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba, como exigência parcial para obtenção do título de Doutor em Ciências Farmacêuticas.

Orientadora: Dr.ª Luciane Cruz Lopes

Sorocaba/SP

2020

Ficha Catalográfica

Fulone, Izabela
F974a Ações e estratégias para o acompanhamento de pacientes com transtornos mentais desinstitucionalizados / Izabela Fulone. – 2020.
199 f. : il.

Orientador: Profa. Dra. Luciane Cruz Lopes.
Tese (Doutorado em Ciências Farmacêuticas) – Universidade de Sorocaba, Sorocaba, SP, 2020.

1. Saúde mental. 2. Esquizofrenia. 3. Medicamentos - Utilização. 4. Política de saúde mental – Brasil. I. Lopes, Luciane Cruz, orient. II. Universidade de Sorocaba. III. Título.

Elaborada por Maria Carla P. F. Gonçalves – CRB-8/6721

Izabela Fulone

AÇÕES E ESTRATÉGIAS PARA O ACOMPANHAMENTO DE PACIENTES COM TRANSTORNOS MENTAIS DESINSTITUCIONALIZADOS

Tese aprovada como requisito parcial para obtenção do grau de Doutor no Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba

Aprovado em: 15/12/2020.

BANCA EXAMINADORA:

Prof.ª Dr.ª Luciane Cruz Lopes
Universidade de Sorocaba - Brasil

Prof. Dr. Helian Nunes de Oliveira
Universidade Federal de Minas Gerais - Brasil

Prof. Dr. Tiago Pereira
Universidade de Leicester – Reino Unido

Prof.ª Dr.ª Denise Razzouk
Universidade Federal de São Paulo - Brasil

Prof. Dr. Ivan Zimmermann
Universidade de Brasília – Brasil

Dedico este trabalho

a Deus,

aos meus pais e à minha vó

(in memorian).

Saudades e amor eterno.

AGRADECIMENTOS

À FAPESP – Fundação de Amparo à Pesquisa do Estado de São Paulo (Processo nº 2017/20668-7) pelo apoio financeiro essencial para realização dessa pesquisa.

À Deus, por todas as bençãos em minha vida, por iluminar meu caminho e me dar força e coragem para seguir.

Aos meus pais (*in memorian*), por todo amor, carinho, dedicação e cuidado. Tenho certeza que estariam muito felizes com essa minha conquista.

Aos meus avós, especialmente à minha vó Zula (*in memorian*), exemplos de seres humanos, que em sua simplicidade me transmitiram os princípios mais sábios da vida.

À minha família, por sempre me apoiar e me incentivar.

Aos meus amigos e todas as pessoas especiais que fazem parte da minha vida, pelo estímulo constante, carinho e bom humor.

Ao meu namorado, pela paciência, incentivo e amor.

À minha querida orientadora, por todos esses anos de convivência, incentivo, dedicação, afeto e confiança. Profissional que inspira e que me faz ter orgulho de ter sido sua aluna de graduação, especialização, mestrado e doutorado. Minha gratidão por todo conhecimento compartilhado!

Ao meu co-orientador, prof. Marcus Tolentino Silva, por não poupar esforços e sabedoria em me ajudar nas análises estatísticas. À prof. Cristiane Bergamaschi e ao prof. Silvio Barberato-Filho, por toda contribuição e solicitude perante minhas dificuldades.

“Um dia, quando olhares para trás, verás que os dias mais belos foram aqueles em que lutastes”

(Sigmund Freud)

RESUMO

Introdução: Embora possam contribuir para melhores desfechos com os cuidados necessários aos pacientes com transtornos mentais graves, o uso sistemático das melhores evidências científicas disponíveis na formulação e implementação de políticas de saúde mental é um dos maiores desafios atuais em sistemas de saúde.
Objetivo: sintetizar e disseminar evidências para melhorar o cuidado de pacientes com transtornos mentais graves desinstitucionalizados e investigar o padrão de uso de antipsicóticos de segunda geração (SGA) dispensados pelo Sistema Único de Saúde (SUS) para tratamento da esquizofrenia e transtornos esquizoafetivos.
Método: utilizou-se as ferramentas de SUPORTE a Ensaios e Revisões relevantes para as Políticas (SUPPORT) para o desenvolvimento da síntese de evidências e de sua disseminação por meio do Diálogo Deliberativo (DD). A investigação do uso de SGA foi conduzida por meio de registros das Autorização de Procedimentos de Alta Complexidade (APAC), armazenados no Sistema de Informação Ambulatorial do SUS (SIA/SUS), entre os anos 2008 a 2017.
Resultados: a busca e a análise crítica na literatura identificaram seis estratégias para melhorar o cuidado de pacientes com transtornos mentais desinstitucionalizados. As deliberações obtidas no DD com importantes *stakeholders* validaram e contribuíram para a disseminação da síntese de evidências. Dentre os usuários de SGA registrados no banco de dados estudado, foram identificados 759.654 pacientes com esquizofrenia ou transtorno esquizoafetivo. Risperidona (33,1%), olanzapina (29,6%), quetiapina (27,7%), ziprasidona (5,1%) e clozapina (4,5%) foram os mais usados. Em idosos, a quetiapina (47,4%) foi a mais utilizada e em crianças, a risperidona (63,3%). A maioria dos pacientes trocaram pelo menos uma vez o SGA e os fatores associados à troca foram: sexo feminino, idade avançada e diagnóstico de transtorno esquizoafetivo ($p < 0,001$ para cada variável). Usuários de risperidona tiveram maior frequência de trocas (58/100 pacientes-ano), enquanto que a clozapina teve a menor frequência de troca (37/100 pacientes-ano). Entre as crianças e adolescentes estudadas (n=49.943), houve diferença de sexo, com predomínio do sexo masculino ($p < 0,001$).
Conclusão A maioria das estratégias identificadas apresentaram correspondências em dispositivos da política de saúde mental brasileira, porém não estavam completamente implementados, dificultando o cuidado desta população. A investigação do uso de SGA gerou informações relevantes sobre o perfil dos usuários, a diferença de sexo, padrão de utilização e de troca de SGA no mundo real, que poderão contribuir para melhorar a prática de cuidados, a gestão, o planejamento e o uso de recursos.

Palavras-chave: Desinstitucionalização. Saúde mental. Serviços comunitários de saúde mental. Esquizofrenia. Transtornos psicóticos. Antipsicóticos. Uso de medicamentos. Medicamentos do Componente Especializado da Assistência Farmacêutica.

ABSTRACT

Introduction: Although can contribute to better outcomes with the necessary care for patients with severe mental disorders, the systematic use of the best scientific evidence available in the formulation and implementation of mental health policies is currently one of the greatest challenges in health systems.
Objective: To synthesize and disseminate evidence to improve the care for deinstitutionalized patients with severe mental disorders and to investigate the use of second- generation antipsychotics (SGA) dispensed by the Brazilian National Health System (SUS) for the treatment of schizophrenia and schizoaffective disorders.
Method: We used the Supporting Policy Relevant Reviews and Trials (SUPPORT) tools to develop the policy brief and to disseminate it through the Deliberative Dialogue (DD). The investigation of the use of SGA was conducted through records related to the Authorization of High Complexity Procedures (APAC), from the Ambulatory Information System (SIA / SUS), between the years 2008 to 2017.
Results: The search and critical analysis in the literature identified six strategies to improve the care for patients with severe mental disorders. The deliberations obtained in the DD with important stakeholders validated and contributed to the dissemination of the synthesis of evidence. Among the users of SGA registered in the database studied, 759,654 patients with schizophrenia or schizoaffective disorder were identified. Risperidone (33.1%), olanzapine (29.6%), quetiapine (27.7%), ziprasidone (5.1%) and clozapine (4.5%) were the most used. In the elderly, quetiapine (47.4%) was the most used, and in children, risperidone (63.3%). Most patients switched the SGA at least once and the factors associated with the switch were: female gender, advanced age, and diagnosis of schizoaffective disorder ($p < 0.001$ for each variable). Risperidone users had the highest frequency of changes (58/100 patient-years), while clozapine had the lowest frequency of change (37/100 patient-years). Among the children and adolescents studied ($n = 49,943$), there was a sex difference, with a predominance of males ($p < 0.001$).
Conclusion: Most of the strategies identified showed correspondence in the Brazilian mental health policy provisions, but not fully implemented, making it difficult to care this population. The investigation of the use of SGA generated relevant information about the profile of users, sex differences, pattern of use, and switch of SGA in the real world, which can contribute to improve the practice of care, management, planning, and use of resources.

Key words: Deinstitutionalization. Mental health. Community mental health services. Schizophrenia. Psychotic disorders. Antipsychotics agents. Drug utilization. Drugs from the Specialized Component of Pharmaceutical Care.

LISTA DE QUADROS

LISTA DE SIGLAS E ABREVIATURAS

ANVISA Agência Nacional de Vigilância Sanitária

APAC Autorização de Procedimentos de Alta Complexidade

BNF British National Formulary

BNFC British Formulary for children

CEAF Componente Especializado da Assistência Farmacêutica

DATASUS Departamento de Informática

DSM-5 Manual de Diagnóstico e Estatístico de Transtornos Mentais 5.ª edição

EVIPNet Rede de Políticas Informadas por Evidencias

FDA *Food and Drug Administration*

MHRA *Medicines and Healthcare products Regulatory Agency*

PCDT Protocolo Clínico e Diretrizes Terapêuticas

SGA Antipsicóticos de segunda geração

SUPPORT SUPORTE a Ensaios e Revisões relevantes para as Políticas *ou Supporting Policy Relevant Reviews and Trials*

SUS Sistema Único de Saúde

SUMÁRIO

1 APRESENTAÇÃO

O presente trabalho constitui tese de Doutorado apresentado ao Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba, linha de pesquisa em Uso Racional de Medicamentos, para obtenção do grau de Doutor em Ciências Farmacêuticas.

O enfoque principal da tese é a saúde mental e inclui o desenvolvimento de ações e estratégias para melhorar o cuidado de pacientes com transtornos mentais desinstitucionalizados e inovações na investigação do uso de antipsicóticos de segunda geração dispensados pelo Componente Especializado da Assistência Farmacêutica para tratamento da esquizofrenia e do transtorno esquizoafetivo.

Esse estudo integra o projeto de pesquisa "**Ações e estratégias para o acompanhamento de pacientes com transtornos mentais desinstitucionalizados na área de abrangência do Departamento Regional de Saúde-XVI, São Paulo",** financiado pela Rede para Políticas Informadas por Evidências (EVIPNet), chamada SCON2017-02502 e o projeto **"Ações e estratégias para o acompanhamento de pacientes com transtornos mentais desinstitucionalizados"**, financiado pela Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), processo no. 2017/20668-7.

A tese foi estruturada com os seguintes elementos: introdução, revisão da literatura, objetivos, resultados no formato de artigos científicos, conforme as recomendações do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (ANEXO A) e considerações finais.

No referencial teórico, discutir-se-á: Políticas públicas informadas por evidências e a tradução do conhecimento; Resgate histórico: dos hospitais psiquiátricos à consolidação do processo de desinstitucionalização de pacientes com transtornos mentais graves; Esquizofrenia e transtorno esquizoafetivo; Recomendações para o tratamento da esquizofrenia e do transtorno esquizoafetivo nos extremos etários (crianças e idosos); Desafios do tratamento para esquizofrenia e transtorno esquizoafetivo e; A importância de banco de dados administrativos em estudos de utilização de medicamentos e para a tomada de decisão em saúde.

A produção científica gerada inclui seis produtos que correspondem aos objetivos dessa tese:

i. Livro: Síntese de evidências para políticas (EVIPNet-Brasil): “Melhorando o cuidado de pacientes com transtornos mentais desinstitucionalizados”;
ii. Artigo científico 1: *“Knowledge translation for improving the care of deinstitutionalized people with severe mental illness in health policy”;*
iii. Artigo científico 2: *“Improving care for deinstitutionalized people with mental disorders: experiences of the use of knowledge translation tools”;*
iv. Artigo científico 3: “*Switching between second-generation antipsychotics in patients with schizophrenia and schizoaffective disorder: 10-year cohort study in Brazil”;*
v. Artigo científico 4: *“Sex differences in the use of atypical antipsychotics in early-onset schizophrenia: a nationwide population-based study in Brazil”;*
vi. Artigo científico 5: “Perfil de utilização de antipsicóticos de segunda geração em pacientes com esquizofrenia atendidos no Sistema Único de Saúde”;

2 INTRODUÇÃO

Aproximadamente um bilhão de pessoas no mundo sofre de algum tipo de transtorno mental (1). A prevalência de transtornos mentais na população adulta brasileira é bastante elevada, variando entre 20-56% (2).

Os transtornos mentais (depressão, ansiedade, transtorno bipolar, esquizofrenia, transtornos do desenvolvimento, transtornos comportamentais da infância, transtornos alimentares) e decorrentes do uso de substancias foram responsáveis por 7,4% do total de carga de doença e por 22,9% do total de anos vividos com incapacidade no mundo (3). No Brasil, representam a terceira causa de carga de doenças, perdendo apenas para as doenças cardiovasculares e cânceres (4, 5).

A reforma psiquiátrica e o processo de desinstitucionalização no Brasil iniciou-se no final da década de 1970 e foi impulsionada por denúncias de maus tratos, violência, falta de assistência nos hospitais psiquiátricos, profundas críticas ao modelo hospitalocêntrico, movimentos antimanicomiais, luta pelos direitos civis de pacientes psiquiátricos, a introdução de antipsicóticos no mercado, crise econômica e necessidade de redução de gastos com internações psiquiátricas (6-8). A promulgação da Lei Federal n° 10.216, de 06 de abril de 2001, acelerou o processo de desinstitucionalização e definiu que a hospitalização seria o último recurso no tratamento dos transtornos mentais e assegurou o direito das pessoas serem tratadas por meio de serviços na comunidade (9).

Os leitos psiquiátricos de longa permanência no Sistema Único de Saúde (SUS) foram reduzidos, muitos hospitais psiquiátricos foram fechados, porém a implementação de uma rede substitutiva e integrada de cuidados efetivos na comunidade para os pacientes desinstitucionalizados não foi totalmente garantida (10, 11).

A desinstitucionalização ocorreu de maneira desigual nas regiões brasileiras e apesar dos avanços obtidos com a criação de Centros de Atenção Psicossocial, Serviços Residenciais Terapêuticos e Programa de Volta para Casa, o processo ainda se encontra em fase de consolidação (6, 12). Diante da magnitude do problema, regiões consideradas grandes polos manicomiais, como Rio de Janeiro, Barbacena, Campina Grande e Sorocaba, enfrentam desafios na construção de uma rede mais densa e diversificada de cuidados efetivos na comunidade (12, 13).

Pessoas com transtornos mentais requerem assistência, uso de psicofármacos e suporte social de maneira contínua, por períodos indeterminados em comunidade (10).

A esquizofrenia é uma doença que contribui consideravelmente para o número de pessoas portadoras de transtorno mental grave e persistente (14, 15). Mais da metade dos pacientes institucionalizados tinham diagnóstico de esquizofrenia e outras psicoses e receberam somente a farmacoterapia com antipsicóticos como manejo clínico (16)

O uso de antipsicóticos representa o pilar do tratamento para esquizofrenia e transtorno esquizoafetivo (17). Fármacos mais antigos, conhecidos como antipsicóticos de primeira geração ou convencionais, como a clorpromazina e o haloperidol, provocaram uma revolução na assistência psiquiátrica quando foram introduzidos no mercado e há mais de 50 anos são usados para tratar esquizofrenia, com benefícios comprovados nos sintomas positivos, porém com efeitos adversos indesejáveis como as reações extrapiramidais (acatisia, discinesia, distonia e parkinsonismo) que podem levar a não adesão, recaídas e hospitalizações (14). Posteriormente, surgiram os antipsicóticos de segunda geração (SGA) com uma proposta de maior efetividade e segurança em relação aos convencionais, por apresentarem menos distúrbios de movimento e reduzirem também os sintomas negativos, cognitivos e afetivos (18). Trata-se de medicamentos mais caros e mais propensos ao ganho de peso e desenvolvimento de síndromes metabólicas (15).

Considerando a falta de evidências sistematizadas sobre políticas públicas para a gestão do cuidado, atrelada ao limitado conhecimento disponível sobre o uso de SGA no cenário de mundo real e nacional, o objetivo deste estudo foi sintetizar e disseminar evidências para melhorar o cuidado de pacientes com transtornos mentais graves desinstitucionalizados e investigar o uso de SGA dispensados pelo SUS para tratamento da esquizofrenia e transtorno esquizoafetivo.

3 REFERENCIAL TEÓRICO

3.1 Políticas públicas informadas por evidência e a tradução do conhecimento

A tradução do conhecimento é um processo dinâmico, interativo e promissor que inclui síntese, disseminação, intercâmbio e aplicação ética de evidências científicas para melhoria da saúde de indivíduos e populações através do fornecimento de serviços e produtos efetivos na saúde (19). Pode representar uma ponte entre pesquisadores e tomadores de decisão.

A necessidade de formular políticas informadas por evidências levou à criação de plataformas de tradução do conhecimento como a Rede de Políticas Informadas por Evidencias (EVIPNet), apoiada pela Organização Mundial da Saúde (20). Atua em nível global, regional e nacional, em países como Ásia, África, Américas, Região do Mediterrâneo Oriental e Europa (21).

A EVIPNet tem como processo de trabalho a tradução e a disseminação de conhecimento a partir dos seguintes passos: i. definição de prioridades para políticas de saúde; ii. busca de evidências para solucionar o problema e definição de opções; iii. elaboração de uma síntese de evidências; iv. realização de um diálogo deliberativo com validação e alinhamento da síntese de evidências; v. considerações sobre implementação de algumas opções e vi. monitoramento e avaliação das ações (22).

A elaboração de uma síntese de evidências e a realização de um diálogo deliberativo deve seguir as ferramentas metodológicas de SUPORTE a Ensaios e Revisões relevantes para as Políticas *(SUPPORT - SUPporting POlicy relevant Reviews and Trials)* (23).

A síntese de evidências é uma forma de tradução e transferência de conhecimento aos tomadores de decisão em um formato mais adequado (24). Reúne evidências globais e locais para deliberações sobre políticas de saúde entre tomadores de decisão e partes interessadas (25). Inclui descrição de um problema, opões para enfrentar o problema, considerações sobre equidade e estratégias para implementação das opções.

O diálogo deliberativo é uma ferramenta interativa para compartilhamento de conhecimento entre tomadores de decisão e partes interessadas. Utiliza a síntese de evidências para subsidiar as deliberações sobre o problema, as opções e as considerações de implementação de acordo com os pontos de vista, as experiências

e o conhecimento dos participantes que estarão envolvidos com futuras decisões sobre uma questão de alta prioridade (26). Importantes atores devem participar do diálogo incluindo tomadores de decisão, trabalhadores da área, pesquisadores, representantes da sociedade civil e dos provedores de serviços. A facilitação do diálogo deve ser feita por um consultor neutro e seguir as regras de *Chatham House* para garantir a não atribuição dos comentários (26).

No Brasil, a EVIPNet surgiu em 2007 e possui diversos grupos de trabalho compostos por representantes de diferentes instituições brasileiras e especialistas convidados de acordo com o tema a ser desenvolvido (24). Seu principal objetivo é estabelecer mecanismos para o uso da melhor evidência científica disponível na tomada de decisão no âmbito do SUS (27).

Ao longo desses anos, as ações da EVIPNet-Brasil foram ampliadas e mostraram resultados positivos como o aumento do número de profissionais capacitados no uso das ferramentas SUPPORT, a conscientização e o interesse em utilizar evidências na formulação de políticas públicas (20, 27). Por outro lado, existem barreiras a serem superadas como a falta de sensibilização dos tomadores de decisão quanto a importância do uso de evidências, interferências socioculturais, falta de interação entre tomadores de decisão, pesquisadores e partes interessadas, reduzido número de síntese de evidências e ausência de centros de respostas rápidas (20). Outros países de média e baixa renda também enfrentam complexos desafios envolvendo escassez de recursos, deficiências na produção e aplicação do conhecimento na prática e no uso de estratégias baseadas em evidências (28).

3.2 Resgate histórico: dos hospitais psiquiátricos à consolidação do processo de desinstitucionalização de pacientes com transtornos mentais graves

A Reforma Psiquiátrica Brasileira teve início no final da década de 1970, tendo como bandeira a luta pela cidadania dos pacientes com transtornos mentais graves e a substituição progressiva dos hospitais psiquiátricos por outras práticas terapêuticas (6). Durante esses anos, inúmeros hospitais psiquiátricos foram objeto de denúncia sobre o desrespeito aos direitos humanos, aos maus tratos a pacientes, à violência, à falta de requisitos mínimos de funcionamento e à falta de assistência (29, 30). Por esses motivos, na década de 1990, vistorias técnicas realizadas pelo recém instituído SUS determinaram o fechamento de inúmeros hospitais psiquiátricos e a assistência

psiquiátrica brasileira passou a ser marcada por uma política de desinstitucionalização, caracterizada pela redução dos leitos em hospitais psiquiátricos e pela implantação de uma rede integral de atenção à saúde mental na comunidade (11). A Lei Federal n° 10.216, de 06 de abril de 2001, acelerou o processo e definiu que a hospitalização é o último recurso no tratamento dos transtornos mentais e assegurou o direito dessas pessoas serem tratadas por meio de serviços na comunidade (9).

Em teoria, desinstitucionalização compreende três componentes: i. Liberação de pessoas que residem em hospitais psiquiátricos para instalações substitutivas na comunidade (por exemplo, os Serviços Residenciais Terapêuticos); ii. Desvio de potenciais novas admissões para instalações substitutivas (por exemplo, Centro de Atenção Psicossocial tipo III e leitos em hospitais gerais), e iii. Serviços especiais para o atendimento de população não institucionalizada com transtorno mental (por exemplo, Centros de Atenção Psicossocial tipo I e II) (31).

Na maioria dos países, os dois primeiros processos avançam muito mais rapidamente do que o terceiro (32). Os censos de hospitais psiquiátricos em todo o país foram reduzidos e novas entradas de paciente foram bloqueadas, mas o terceiro processo é crítico, uma vez que a oferta adequada, de qualidade e acessível de serviços substitutivos e complementares à hospitalização para a comunidade é insuficiente e frágil (6).

Na década de 1990, havia 72.514 leitos psiquiátricos SUS. Em 2001, os leitos foram reduzidos para 52.962 e em 2014, o Brasil apresentava 25.988 leitos psiquiátricos distribuídos em 116 municípios (6, 33). O Censo Psicossocial do Estado de São Paulo de 2014 identificou 53 hospitais psiquiátricos em 14 Departamentos Regionais de Saúde (DRS), sendo sete deles na região de Sorocaba, pertencente ao DRS-XVI (33). Em 2016, um dos maiores polos manicomiais do Brasil, região de Sorocaba, ainda existiam 460 pacientes internados no Hospital Psiquiátrico Vera Cruz (34).

A contenção e a reclusão devem ser evitadas sempre que possível. Pesquisas mostram que a maioria dos pacientes desinstitucionalizados são capazes de viver em comunidade com programas adequados de suporte (35). A acessibilidade a serviços baseados em evidências para reinserir/ adaptar a vida na comunidade, aumentar a autonomia, melhorar a função social e familiar, bem como ações farmacoterapêuticas

apropriadas para controlar os sintomas, são elementos chaves para o sucesso da transição do hospital para a comunidade (36, 37).

Nos últimos anos, o SUS vem se empenhando para a concretização das diretrizes de superação do modelo de atenção centrado no hospital e para a efetiva reintegração das pessoas com transtornos mentais graves. A política de saúde mental do Ministério da Saúde está sendo desenhada a partir da implementação e financiamento de alguns dispositivos estratégicos na área de saúde mental, tais como Serviços Residenciais Terapêuticos, Programa de Volta para Casa, Centros de Atenção Psicossocial, Centros de Convivência e Cultura, Programa de Reestruturação dos Hospitais Psiquiátricos e iniciativas de geração de trabalho (33). Polos manicomiais, como a região de Sorocaba, vem mudando sua história e construindo uma rede diversificada de serviços. No entanto, o êxito neste processo e sua distribuição ainda são desiguais e apresenta-se em curso (12).

Ao longo dessas quatro décadas de mudanças e avanço, algumas limitações chaves não foram superadas, como o subinvestimento na área de saúde mental e a difícil articulação da Rede de Atenção Psicossocial com a Atenção Básica, que em muitas situações parece rejeitar os casos de saúde mental (38). Atualmente, vivenciamos importantes desafios e paradoxos em relação a reforma psiquiátrica, devido a tendência de interesses ligados à mercantilização da vida e ao resgate dos manicômios, que representaria um trágico retrocesso (7).

3.3 Esquizofrenia e transtorno esquizoafetivo

3.3.1 Epidemiologia e etiopatogenia

A esquizofrenia é um transtorno psiquiátrico crônico caracterizado pela combinação de sintomas comumente divididos em sintomas positivos e negativos (39). Os sintomas positivos incluem delírios, alucinações, comportamento desorganizado, comportamentos motores catatônicos e distorções de pensamento e fala (17). Os sintomas negativos refletem a diminuição ou perda das funções normais como embotamento afetivo, alogia, abulia e anedonia (39).

O diagnóstico de esquizofrenia exige que pelo menos dois sintomas positivos ou negativos estejam presentes por pelo menos um mês (fase ativa) e que alguns destes sintomas persistam por até seis meses (40).

Acomete ligeiramente mais homens do que mulheres (razão de risco de homens para mulheres é 1,4:1) (17) e ocorre geralmente no final da adolescência e início da fase adulta (41). Nas mulheres, os sintomas aparecem antes dos 35 anos e nos homens antes dos 25 anos de idade, sendo raro o início antes da adolescência (17). O sexo parece ser um fator preditivo no curso e na evolução da doença. Estudos tem revelado diferença de sexo na prevalência da esquizofrenia, com predomínio do sexo masculino (42, 43).

A prevalência global varia entre 0,3% a 0,7% de acordo com a raça e localização geográfica (41). Parece ser mais frequente em afro-americanos e asiáticos-americanos do que em outros grupos raciais e apresentam maior incidência entre populações urbanas e de menor renda do que em populações rurais com maior renda (17, 44). Pacientes com esquizofrenia apresentam maiores taxas de morbidade e mortalidade, com expectativa de vida de 15 a 20 anos mais curta do que a população geral, devido a problemas cardiovasculares, cânceres, acidentes e suicídios (17). Déficits cognitivos incluindo problemas de atenção, linguagem, memória e função executiva, tendem a aparecer antes e durante o desenvolvimento do transtorno (44).

Fatores genéticos, ambientais, alterações bioquímicas e cerebrais influenciam o aparecimento e o desenvolvimento da esquizofrenia (45). Um indivíduo com vulnerabilidade biológica específica (hereditariedade), sob influência de constantes fatores estressores, pode desenvolver sintomas esquizofrênicos ao longo do tempo (44, 45). Esses fatores estressores podem ser ambientais (perdas e traumas), biológicos (infecções e uso abusivo de determinadas substâncias psicoativas) ou ambos (17).

Sua fisiopatologia também não é completamente conhecida (17, 41, 44). Uma das hipóteses mais aceitas consiste em alterações bioquímicas e anormalidades estruturais do cérebro (39). As alterações bioquímicas envolvem principalmente alterações no sistema dopaminérgico (hiperfunção dopaminérgica) (44). Este sistema se distribui na região nigroestriatal, mesolímbico, mesocortical e túberoinfundibular, as quais estão relacionadas a movimentos involuntários, funções cognitivas e emocionais, secreção de alguns hormônios sexuais e hipofisários, como prolactina (39). Além disso, ocorrem alterações na atividade serotoninérgica, glutaminérgica e gabaérgica (46). As anormalidades cerebrais incluem redução do volume cerebral global, com diminuição da amígdala, hipocampo, córtex frontal e estruturas subcorticais, aumento dos ventrículos cerebrais e disfunções hemisféricas (17, 45).

O transtorno esquizoafetivo compartilha algumas características da esquizofrenia e dos transtornos de humor (15). O diagnóstico é controverso e vários autores debatem se o transtorno esquizoafetivo é uma forma de esquizofrenia ou de transtorno afetivo ou uma condição distinta (47). O Manual de Diagnóstico e Estatístico de Transtornos Mentais 5.ª edição (DSM-5) o define como um transtorno distinto, caracterizado pela presença concomitante de sintomas de humor (maníaco, depressivo ou ambos) e sintomas psicóticos (da fase ativa) durante um período de aproximadamente um mês (44).

Ao longo dos anos, mais da metade dos pacientes com transtorno esquizoafetivo migram para o diagnóstico de esquizofrenia (48). A principal diferença entre esquizofrenia e transtorno esquizoafetivo parece estar na duração dos sintomas de humor que tende a ser mais breve na esquizofrenia (44).

Estima-se que o transtorno esquizoafetivo seja menos comum do que a esquizofrenia e acometa mais homens do que mulheres, com início antes dos 30 anos (15). Faltam dados específicos sobre a etiologia e a fisiopatologia do transtorno esquizoafetivo, pois a maioria dos estudos o inclui com os transtornos esquizofrênicos ou bipolares (15, 47).

3.3.2 Manejo terapêutico: os antipsicóticos e seus desfechos de efetividade e segurança

O tratamento farmacológico da esquizofrenia iniciou-se na década de cinquenta com a descoberta dos antipsicóticos e provocou uma revolução na área da psiquiatria, pois permitiu que parte dos pacientes institucionalizados em hospitais psiquiátricos pudessem ser tratados na comunidade (16, 39, 45).

Os primeiros fármacos com efetividade comprovada para tratar a esquizofrenia e outros distúrbios psicóticos são os antipsicóticos de primeira geração, típicos ou convencionais (por exemplo, clorpromazina, haloperidol, flufenazina, tioridazina) que apresentam como mecanismo de ação o bloqueio de neuroreceptores de dopamina-2, que reduz os sintomas positivos (39). Estão associados a efeitos adversos indesejáveis como sintomas extrapiramidais (acatisia, parkinsonismo e distonia, tremor), discinesia tardia, sedação e efeitos anticolinérgicos (constipação, visão turva e retenção urinária) (18).

Em busca de fármacos que não apresentassem os mesmos efeitos adversos indesejáveis dos antipsicóticos convencionais e ainda atuassem nos sintomas negativos, surgiram na década de 1980, os SGA ou também conhecidos, como atípicos (por exemplo, clozapina, olanzapina, quetiapina, ziprasidona, risperidona, aripripazol). Estes antipsicóticos apresentam como principal vantagem em relação aos convencionais, menos distúrbios de movimento/extrapiramidais e menor incidência de efeitos anticolinérgicos (49). Estão associados ao risco de desenvolver síndrome metabólica, ganho de peso e diabetes (49, 50). Especificamente em relação a clozapina, há um risco de 0,8% de agranulocitose e mais raramente de íleo paralítico (51).

O uso de antipsicóticos de primeira ou segunda geração representa o pilar do tratamento para esquizofrenia e outros distúrbios psicóticos, incluindo o transtorno esquizoafetivo (52). Na fase aguda, estes medicamentos são empregados para aliviar sintomas positivos, prevenir possíveis danos advindos da agressividade e melhorar o funcionamento social dos pacientes (14). Na fase de manutenção, o objetivo é reduzir recaídas, melhorar o funcionamento e a qualidade de vida (53).

Com benefício clínico definido, o uso de antipsicóticos em geral reduz as recaídas, diminui a taxa de hospitalização e melhora a qualidade de vida dos pacientes durante a fase de manutenção do tratamento quando comparado a placebo (54).

Evidências mostram que não há diferenças de efetividade entre os antipsicóticos atípicos, exceto a clozapina (55, 56). As diferenças residem no perfil de efeitos adversos a curto e longo prazo. A escolha do antipsicótico deve ser baseada na história clínica do paciente e nos possíveis efeitos adversos: metabólicos (ganho de peso, aparecimento de diabetes); extrapiramidais (acatisia, discinesia e distonia); cardiovasculares (prolongamento do intervalo QT); hormonais (aumento da prolactina plasmática) e sedação (52).

O uso de olanzapina em pacientes com esquizofrenia, transtorno esquizoafetivo ou esquizofreniforme quando comparado ao uso de outros SGA (clozapina, risperidona, olanzapina, quetiapina, aripiprazol e amissulpirida) associou-se mais frequentemente a ganho de peso e síndromes metabólicas (alterações da glicose e do colesterol) do que os outros grupos, exceto a clozapina. A olanzapina também foi ligeiramente mais eficaz do que aripiprazol, quetiapina, risperidona e ziprasidona (49).

Quetiapina também foi comparada a outros SGA (clozapina, olanzapina, risperidona, ziprasidona, paliperidona e aripiprazol) e exibiu menos efeitos extrapiramidais e menor taxa de hiperprolactinemia. Especificamente em relação a ziprasidona, a quetiapina produziu mais sedação, ganho de peso e aumento dos níveis de colesterol. Porém, a quetiapina produz menos ganho de peso do que a olanzapina (57).

Ziprasidona apresentou menor aceitabilidade do que a olanzapina e risperidona. Apesar das evidências serem limitadas, este fármaco parece ser ligeiramente menos eficaz do que olanzapina e risperidona e está associado a menor ganho de peso (58).

A risperidona foi comparada a outros SGA (amissulprida, aripiprazol, clozapina, olanzapina, quetiapina, sertindol, ziprasidona or zotepina) e associou-se a maior incidência de efeitos extrapiramidais e aumento dos níveis de prolactina. Porém, provocou menos distúrbios metabólicos e ganho de peso comparado à olanzapina, quetiapina e clozapina (59).

A clozapina se mostrou mais efetiva do que os outros SGA em pacientes com esquizofrenia resistente ao tratamento, particularmente nos sintomas positivos, em curto e longo prazo (55, 56). Para sintomas negativos, a clozapina foi superior somente em curto prazo (55). Estudo de coorte conduzido na Suécia com pacientes diagnosticados com esquizofrenia mostraram que os usuários de clozapina apresentaram maior aderência ao tratamento, menor taxa de hospitalização e de morte por suicídio (60). A clozapina foi associada à agranulocitose, sialorreia, sedação e maior risco de convulsões do que olanzapina, risperidona e quetiapina (56). Além disso, produz maior incidência de alterações eletrocardiogramas e maior ganho de peso do que a risperidona (56).

O risco de provocar agranulocitose, podendo ser fatal, explica o fato da clozapina ter sido retirada do mercado logo depois de seu lançamento no mercado em 1970. Porém, na década de 1980, ela é reintroduzida no mercado por seu efeito antipsicótico superior em casos de esquizofrenia refratária e desde então requer monitoramento hematológico apropriado (14).

3.*3*.3 Protocolos clínicos e diretrizes internacionais

Diretrizes Clínicas do Canadá, Espanha, Reino Unido, Austrália e Nova Zelândia recomendam como primeira linha de tratamento o uso de SGA por apresentar menos efeitos extrapiramidais e também por associar-se à maior aderência ao tratamento e a melhores benefícios clínicos. A clozapina é reservada para casos refratários e só deve ser usada após falha terapêutica de dois outros antipsicóticos (14, 52).

BMJ Best Practice também recomenda dar preferência para SGA devido a menor taxa de efeitos adversos. Entretanto, se o paciente tiver usando um antipsicótico de primeira geração e apresentar melhora clínica significativa, sem efeitos adversos intoleráveis, não é recomendada a troca para SGA (17).

Pacientes em primeiro episódio ou que tenham sido diagnosticados recentemente não devem usar clozapina como primeira opção e devem seguir o tratamento com outro SGA, por pelo menos um ano, em doses mais baixas (17). Em pacientes refratários, a clozapina também só deve ser prescrita depois de duas tentativas sem sucesso com antipsicóticos diferentes (41). Exceção pode ocorrer em casos com alto risco de suicídio e discinesia tardia de repercussão significativa (69).

Estudos examinaram as recomendações em comum e as disparidades entre as diretrizes clínicas para esquizofrenia e comprovaram que existe consenso na primeira linha de tratamento (SGA, exceto clozapina), na indicação da clozapina em casos refratários e na duração do tratamento na fase de manutenção (no mínimo 1 a 2 anos) (53, 61).

Por outro lado, a escolha inicial do SGA é incerta. A olanzapina geralmente não é considerada como primeira escolha, provavelmente devido ao ganho de peso, sendo recomendada para a fase de manutenção (62, 63). Algumas diretrizes recomendam a risperidona como terapia inicial, outras a recomendam na fase de manutenção (64, 65).

Outras discrepâncias concentraram-se no tempo de tratamento da fase aguda de pacientes que apresentaram o primeiro episódio (variando de 2 a 12 semanas) e no tempo de tratamento da fase de manutenção daqueles pacientes que apresentaram múltiplos episódios (variando de 2 a 5 anos) (15, 53). Em casos mais graves, o tempo de tratamento é indeterminado, podendo seguir por toda a vida (17).

Recomendações sobre dose variam entre as diretrizes. Entretanto, sugere-se iniciar o tratamento na menor dose, se possível, e ser titulada ao longo do tratamento, a fim de garantir resposta terapêutica ótima e detectar precocemente o aparecimento

de potenciais efeitos adversos como efeitos extrapiramidais, ganho de peso e insônia (14). Apesar das evidências serem limitadas, é comum empregar altas doses para tentar atingir um benefício clínico (66).

O uso de antipsicóticos de primeira geração na forma injetável deve ser indicado para pacientes com baixa adesão ao tratamento oral ou para aqueles que apresentam história de abuso de drogas (14, 17).

A maioria dos estudos que investigam a farmacoterapia para esquizofrenia também incluem pacientes com transtorno esquizoafetivo, apresentando respostas clínicas semelhantes, portanto as linhas de tratamentos são semelhantes (47). Quando necessário, estabilizadores de humor e antidepressivos podem ser combinados à terapia com antipsicóticos (47, 67). Ressalta-se que não há evidências específicas sobre o tratamento de pacientes com transtorno esquizoafetivo (48, 67).

3.3.4 Protocolos Clínicos e Diretrizes Terapêuticas Brasileiras

Em 2002, o Brasil estabeleceu o primeiro Protocolo Clínico e Diretrizes Terapêuticas (PCDT) para tratamento da esquizofrenia refratária, preconizando os critérios de diagnóstico, os critérios de inclusão/exclusão de pacientes no tratamento, esquema terapêutico, mecanismos de acompanhamento e avaliação deste tratamento (68). Houve uma atualização deste protocolo em 2013, que se encontra em vigor até os dias atuais (69). Essas diretrizes terapêuticas são de caráter nacional e devem ser seguidas pelas Secretarias de Saúde dos Estados, do Distrito Federal e dos municípios para dispensação dos medicamentos nele previstos. Enfatizamos os SGA pertencentes ao Componente Especializado da Assistência Farmacêutica: clozapina, olanzapina, risperidona, quetiapina e ziprasidona.

Este primeiro PCDT incluiu os seguintes diagnósticos de acordo com a Classificação Internacional de Doenças e Problemas relacionados à Saúde, décima versão (CID-10): esquizofrenia paranoide (F20.0), esquizofrenia hebefrênica (F20.1), esquizofrenia catatônica (F20.2) e indiferenciada (F20.3). Para ser incluído neste protocolo, o paciente deveria ter como diagnóstico primário uma das CID citadas, ter apresentado falha terapêutica à maior dose tolerada pelo paciente de pelo menos dois antipsicóticos convencionais ou de primeira geração (por exemplo, clorpromazina ou haloperidol) ou apresentar problemas sérios de tolerabilidade. A partir disso, recomendava-se tratar com risperidona. Caso houvesse falha ou contraindicação,

usar clozapina. Na impossibilidade de usar clozapina ou de ter ocorrido novamente uma falha terapêutica, recomendava-se trocar para quetiapina, olanzapina ou ziprasidona (68).

A última atualização deste PCDT ocorreu em 2013 e trouxe algumas modificações. Houve a inclusão de outras CID além daquelas apresentadas no primeiro protocolo, tais como: depressão pós-esquizofrênica (F20.4), esquizofrenia residual (F20.5), esquizofrenia simples (F20.6) e outras esquizofrenias (F20.8) (25). A lista de SGA permaneceu a mesma, porém o esquema de tratamento teve algumas alterações. Preconiza-se ainda o uso de antipsicóticos em monoterapia, de acordo com o perfil de tolerabilidade e segurança do paciente, sem ordem de preferência, podendo ser utilizado qualquer antipsicótico disponível no SUS, exceto a clozapina. Esta só deve ser considerada em pacientes refratários, após ter usado pelo menos dois outros antipsicóticos (risperidona, olanzapina, quetiapina ou ziprasidona), por pelo menos 6 semanas, nas doses adequadas e se não houver melhora de pelo menos 30% na escala de Avaliação Psiquiátrica Breve (*Psychiatric Rating Scale – BPRS*) (69). A preparação de depósito do haloperidol (injetável) deve ser utilizado somente em pacientes que não aderem ao tratamento por via oral (69).

O Quadro 1 mostra os antipsicóticos apresentados no PCDT (2013) e sua respectiva apresentação farmacêutica:

Quadro 1 - Antipsicóticos presentes no Protocolo Clínico e Diretrizes Terapêuticas para tratamento da esquizofrenia.

Antipsicóticos de primeira geração	**Apresentação farmacêutica**
clorpromazina	comprimidos de 25mg e 100mg; solução oral de 40mg/mL
haloperidol	comprimidos de 1mg; 5mg; solução oral 2mg/mL
decanoato de haloperidol	solução injetável 50mg/mL
Antipsicóticos de segunda geração[&]	**Apresentação farmacêutica**
clozapina	comprimidos de 25mg e 100mg
olanzapina	comprimidos de 5mg e 10mg;
risperidona	comprimidos de 1mg, 2mg e 3mg;
quetiapina	comprimidos de 25mg, 100mg, 200mg e 300mg
ziprasidona	cápsulas de 40mg e 80mg;

[&] contemplados pelo Componente Especializado da Assistência Farmacêutica

Fonte: Elaboração própria

Antes de iniciar o tratamento com qualquer antipsicótico, é necessário investigar a história familiar ou prévia de síndrome neuroléptica maligna, distonia/discinesia, tentativa de suicídio, obesidade, doenças cardiovasculares,

doenças cerebrovasculares, diabetes, câncer de mama, hiperprolactinemia, epilepsia, doença de Parkinson e Alzheimer. O paciente incluído neste PCDT, dever ter suas medidas antropométricas, pressão arterial, níveis de colesterol total, triglicerídeos, prolactina e glicemia de jejum avaliadas (69).

Para monitorização dos efeitos adversos, o PCDT incluiu como medidas obrigatórias: medidas antropométricas e de pressão arterial em 3, 6 e 12 meses; exames laboratoriais de perfil lipídico e glicemia de jejum em 3 e 12 meses. Após esse período, a monitorização deve ser feita anualmente. A dosagem do nível sérico de prolactina deve ser solicitada sempre que houver relato de sintomas compatíveis com alterações hormonais, tais como galactorréia, alterações menstruais, diminuição da libido e impotência. Para os pacientes que fazem uso de clozapina, é necessário a realização de hemograma completo a intervalos semanais e cada aumento de dose nas primeiras 18 semanas de tratamento e depois, em intervalos mensais ao longo de todo o tempo de tratamento. Como o tempo de tratamento para a esquizofrenia é indeterminado, o acompanhamento dos pacientes deve ser feito a cada 6 meses, a fim de reavaliar a efetividade e a segurança do tratamento (69).

Devido à falta de estudos específicos, o PCDT para transtorno esquizoafetivo considera o uso de antipsicóticos como primeira linha de tratamento e segue as mesmas recomendações e esquemas terapêuticos apresentados no PCDT para esquizofrenia (48).

3.4 Recomendações para o tratamento nos extremos etários

As evidências sobre a efetividade e segurança do uso de antipsicóticos para tratamento da esquizofrenia em faixas etárias extremas (crianças e idosos) são limitadas e baseadas em pequenos estudos, uma vez que esses indivíduos geralmente são excluídos dos ensaios clínicos (70-72).

O Brasil não tem protocolo específico para tratamento da esquizofrenia ou transtorno esquizoafetivo em crianças, adolescentes e idosos (69). As recomendações apresentadas no protocolo para adultos geralmente são extrapoladas para o tratamento de crianças e idosos. Apesar de existir importantes diferenças, a maioria das diretrizes internacionais direcionadas a esses grupos são adaptações de diretrizes já existentes para adultos devido a lacuna de evidências específicas (73, 74)

As crianças que apresentam esquizofrenia de início precoce (antes dos 18 anos) são potencialmente mais susceptíveis aos efeitos adversos dos antipsicóticos e a escolha do antipsicótico deve ser feita de acordo com o perfil metabólico, cardiovascular e hormonal da criança (73). Diretrizes do Reino Unido e Estados Unidos recomendam iniciar o tratamento com SGA, como a risperidona e aripiprazol em crianças (74, 75).

De acordo com as agências regulatórias do Brasil (ANVISA), Estados Unidos (FDA) e Reino Unido (MHRA) (76-78), a maioria dos SGA não são aprovados para tratamento de esquizofrenia em crianças, conforme mostra o Quadro 2.

Quadro 2: Aprovação do uso de antipsicóticos para tratamento da esquizofrenia em agências reguladoras do Brasil (ANVISA), Estados Unidos (FDA) e Reino Unido (MHRA).

Fármaco	**Aprovação de uso em crianças e adolescentes**		
	ANVISA*(77)	**FDA&(76)**	**MHRA#(78)**
clozapina	a partir de 18 anos	a partir de 18 anos	a partir de 16 anos
olanzapina	a partir de 13 anos	a partir de 13 anos	a partir dos 12 anos
risperidona	a partir de 13 anos	a partir 13 anos	a partir dos 12 anos
quetiapina	a partir de 13 anos	a partir de 13 anos	a partir dos 12 anos
ziprasidona	a partir de 18 anos	a partir de 18 anos	não comercializado

*Agência Nacional de Vigilância Sanitária, Brasil; & *Food and Drug Administration,* Estados Unidos;
Medicines and Healthcare products Regulatory Agency, Reino Unido.

Fonte: Elaboração própria

Entretanto, estudos de várias partes do mundo tem mostrado um aumento significativo do uso desses antipsicóticos em crianças e adolescentes (79-81). O uso *off-label* é uma prática comum e pode estar inflacionando o consumo, mesmo sabendo das lacunas existentes envolvendo a efetividade, segurança e efeitos a longo prazo (82, 83).

Recomenda-se iniciar o tratamento em crianças e adolescentes com baixas doses de antipsicóticos e ir aumentando gradualmente (78). Como o metabolismo nessa faixa etária é mais rápido, em alguns casos é necessário utilizar doses mais altas (74). Mas, até o momento não há evidências convincentes sobre a efetividade

de se utilizar doses mais baixas ou doses padrão ou doses mais altas em adolescentes (71).

O Quadro 3 mostra as doses recomendadas pelo protocolo clínico brasileiro para tratamento da esquizofrenia em adultos e as doses recomendadas pelo *British National Formulary* (BNF) para crianças/ adolescentes (12-17 anos).

Quadro 3: Doses recomendadas dos SGA para tratamento da esquizofrenia (dose mínima – dose máxima).

Fármaco	Protocolo Clínico Brasileiro para adultos[69] (mg/dia)	*British National Formulary for children*[78] - 12 a 17 anos (mg/dia)	DDD (mg)
clozapina	12,5 – 800	12,5 – 900	300
olanzapina	5 – 30	5 – 20	10
risperidona	1 – 6	2 – 16	5
quetiapina	25 – 800	25- 750	400
ziprasidona	40 – 160	não comercializado	80

Fonte: Elaboração própria

O tratamento da esquizofrenia tardia (em indivíduos com idade avançada) também é guiado pelos resultados de ensaios clínicos conduzidos com pessoas mais jovens. Entretanto, as mudanças fisiológicas decorrente da idade avançada pode resultar em prolongamento do efeito dos antipsicóticos e maior susceptibilidade a efeitos adversos (72).

Os SGA parecem ser bem tolerados pelos idosos desde que eles tenham baixo potencial para efeitos extrapiramidais, distúrbios metabólicos e ganho de peso (72). De acordo com o critério de Beers, os SGA devem ser utilizados com cautela e em doses mais baixas (40). Um estudo de coorte retrospectiva mostrou associação entre o uso de antipsicóticos (primeira e segunda geração) e risco de morte e parada cardiorrespiratória em idosos hospitalizados acima de 65 anos, porém mais estudos são necessários (84).

3.5 Desafios do tratamento da esquizofrenia e transtorno esquizoafetivo

A não aderência ao tratamento medicamentoso é comum e pode ser uma das principais causas de recaídas, hospitalizações e prognósticos desfavoráveis (85).

Metade dos pacientes portadores de doenças crônicas não adere ao tratamento, principalmente aqueles com transtornos mentais (86).

Os fatores associados à não aderência são múltiplos e podem estar relacionados a efeitos adversos, falha terapêutica, falta de suporte (familiar/cuidador), prejuízos cognitivos e problemas relacionados ao sistema de prestação de serviços de saúde (87). A falha terapêutica, a falta de tolerabilidade a certos efeitos adversos ou a inaceitabilidade do tratamento pode determinar a troca de medicamento (88).

Substituir um antipsicótico por outro com perfil de efetividade e segurança mais favorável é uma estratégia recomendada, a fim de otimizar o tratamento (89, 90). Recomenda-se no mínimo duas semanas de uso, sem melhora clínica, para interromper o tratamento com um antipsicótico e trocá-lo por outro (17). No entanto, deve-se balancear o estado clínico do paciente e as características farmacológicas e farmacocinéticas do atual e do novo antipsicótico a ser prescrito. A substituição está associada a crises, desestabilização do paciente, recaídas, hospitalizações e consequentemente, a custos inflacionados (91, 92). Além disso, a troca pode apresentar outras desvantagens como possíveis interações medicamentosas graves, potencial para reações adversas combinadas, risco de toxicidade e efeitos decorrentes da retirada do medicamento (92).

Alguns desfechos negativos ocasionados por alguns tipos de troca abrupta já estão documentados incluindo insônia rebote (troca entre um agente mais sedativo por outro menos sedativo), reações adversas relacionadas ao rebote colinérgico como náuseas, vômito, agitação, sudorese excessiva e diarreia (troca entre um antipsicótico com alta afinidade por receptores muscarínicos por outro com baixa afinidade) e efeito rebote de efeitos extrapiramidais (62, 92).

A estratégia ideal de troca que representaria menor risco aos pacientes, envolveria um intervalo sem medicamento (*wash out*) ao fazer a substituição. Mas, isso geralmente não é viável para este tipo de paciente, pois o risco de recaída é alto. Apesar de ser uma prática comum, existem poucos estudos sobre a troca de antipsicóticos (90). Há um *gap* de evidências sobre quais estratégias são mais efetivas e seguras (93). Estudos são necessários para investigar quando e como as trocas podem ser feitas adequadamente, baseados na melhor evidência disponível.

3.6 A importância de banco de dados administrativos em estudos de utilização de medicamentos e para a tomada de decisão em saúde

Ensaios clínicos randomizados podem fornecer dados de efetividade e segurança de fármacos por um período curto de tempo, a partir de uma amostra relativamente pequena, sem a participação de indivíduos altamente vulneráveis, como crianças e idosos. Por outro lado, estudos epidemiológicos que utilizam grandes bancos de dados em saúde *(big data)* podem revelar evidências robustas de utilização de medicamentos em diversos cenários da vida real e responder várias questões clínicas aos médicos e pacientes (94). Atualmente, muitos bancos de dados administrativos estão sendo utilizados para investigar a qualidade da prescrição, a aderência ao tratamento, a efetividade e segurança do uso de medicamentos em idosos, crianças e gestantes, e para análises de custo (94). Banco de dados provenientes de prontuários médicos eletrônicos também representa uma valiosa ferramenta, pois proporciona a trajetória virtual médica completa dos pacientes (95).

A validade dessas investigações dependerá da qualidade e da integridade do registro dos dados (94). Registros incompletos e mal codificados, seja por engano ou por erro, ausência de detalhamento na descrição clínica e não preenchimento de campos não obrigatórios podem comprometer a análise e a validade do estudo.

O Brasil possui potenciais bancos de dados que armazenam informações relacionadas a saúde, gerados principalmente a partir de dados do SUS (96). Esses dados são gerenciados pelo Ministério da Saúde e organizados pelo seu Departamento de Informática (DATASUS). O DATASUS é composto por diversos sistemas que abrangem dados ambulatoriais, hospitalares, epidemiológicos e informações sobre a rede de assistência à saúde, entre outros (97).

O sistema de informações ambulatoriais do SUS (SIA) é responsável pela captação e processamento das contas ambulatoriais do SUS. Seu subsistema, Autorização de Procedimentos de Alta Complexidade (APAC), registra os procedimentos ambulatoriais e fornecimento de medicamentos pertencentes ao Componente Especializado da Assistência Farmacêutica (CEAF), totalizando mais de 200 milhões de atendimentos mensais (98).

O CEAF é *“uma estratégia da Política Nacional da Assistência Farmacêutica, caracterizada pela busca da integralidade do tratamento medicamentoso, em nível ambulatorial, cujas linhas de cuidado estão definidas nos Protocolos Clínicos e*

Diretrizes Terapêuticos publicados pelo Ministério da Saúde" (99). Surgiu em 2010 em substituição ao Componente de Medicamentos de Dispensação Excepcional, conhecidos popularmente como medicamentos de alto custo, cujo financiamento é responsabilidade da União e das Unidades Federativas (100).

Para solicitação dos medicamentos pertencentes ao CEAF, é necessário o preenchimento de um formulário oficial padronizado pelo Ministério da Saúde (100). A autorização será concedida após avaliação realizada em conformidade com o protocolo clínico publicado pelo Ministério da Saúde (101). Posteriormente, todos os dados de solicitação de medicamentos são registrados na Apac e a dispensação do medicamento ao paciente ocorre mensalmente, por um período de três meses, na farmácia onde foi efetuada a solicitação (101). Após esse prazo, se necessário, o processo deve ser renovado.

O Brasil vem apresentando iniciativas com o uso de grandes bancos de dados provenientes do SUS (*big data*) e buscando integração entre os bancos de dados (*record linkage*) (91, 102, 103). Apesar do potencial dos bancos de dados brasileiros, estes ainda não são integrados entre si e a maior parte deles tem acesso restrito, fato que dificulta o avanço da pesquisa (96).

4. OBJETIVOS

4.1 Objetivo geral

Sintetizar e disseminar evidências para melhorar o cuidado de pacientes com transtornos mentais graves desinstitucionalizados e investigar o padrão de uso de antipsicóticos de segunda geração, dispensados pelo Sistema Único de Saúde para tratamento da esquizofrenia e transtorno esquizoafetivo.

4.2 Objetivos específicos

Parte I

- ✓ Sintetizar evidências para o planejamento de políticas que melhorem o cuidado e o acompanhamento de pacientes com transtornos mentais graves desinstitucionalizados.

- ✓ Traduzir o conhecimento criticamente sistematizado e analisado por meio de diálogo com *stakeholders*.

Parte II

- ✓ Investigar a utilização de antipsicóticos de segunda geração para o tratamento de esquizofrenia e transtorno esquizoafetivo no Sistema Único de Saúde de 2008 a 2017.

5. RESULTADOS

5.1 Produtos da Parte I

5.1.1 Livro – Melhorando o cuidado de pacientes com transtornos mentais desinstitucionalizados: síntese de evidências para políticas de saúde

O livro “Melhorando o cuidado de pacientes com transtornos mentais desinstitucionalizados: síntese de evidências para políticas de saúde” incluiu a contextualização e a descrição do problema (desinstitucionalização), identificação de opções políticas viáveis e efetivas para solucionar o problema, considerações sobre possíveis barreiras de implementação das opções, facilitadores e equidade.

Este produto (ISBN: 978-85-334-2769-3) foi elaborado de acordo com o método oferecido pela EVIPNet-Brasil e foi publicado pelo Ministério da Saúde na versão eletrônica em maio de 2020. Está disponível no seguinte endereço: http://bvsms.saude.gov.br/bvs/publicacoes/sintese_evidencias_pacientes_transtornos_mentais.pdf

A capa do livro publicado encontra-se no ANEXO B.

A seguir, será apresentado o resumo informativo da síntese de evidências e a formatação seguiu as normas da EVIPNet-Brasil.

Resumo informativo da síntese de evidências: “Melhorando o cuidado de pacientes com transtornos mentais desinstitucionalizados

Autores:

Izabela Fulone[1]

Cristiane de Cassia Bergamaschi Motta[1]

Silvio Barberato-Filho[1]

Marcus Tolentino Silva[1]

Luciane Cruz Lopes[1]

[1]Programa de Pós-Graduação stricto sensu em Ciências Farmacêuticas - Universidade de Sorocaba – UNISO

Contexto e antecedentes:

Na década de 1980, a história da saúde mental brasileira foi marcada por graves denúncias de maus tratos, falta de higiene e de cuidados aos pacientes com transtornos mentais que viviam em hospitais psiquiátricos. Mobilizações sociais e políticas impulsionaram o processo de desinstitucionalização, ou seja, a substituição progressiva dos hospitais psiquiátricos por outras práticas terapêuticas (BRASIL, 2005). A Lei Federal n° 10.216/01 acelerou esse processo e definiu que a hospitalização é o último recurso no tratamento dos transtornos mentais e assegurou o direito das pessoas a serem tratadas por meio de serviços na comunidade (BRASIL, 2001).

Os leitos psiquiátricos foram reduzidos e novas práticas de cuidado comunitário foram construídas (WHO, 2014). A região de Sorocaba, pertencente ao Departamento Regional de Saúde (DRS-XVI), já foi considerada um dos maiores polos manicomiais do país devido à alta concentração de leitos psiquiátricos (CAYRES et al., 2015; GARCIA, 2012).

O alto índice de mortalidade dentro dos hospitais psiquiátricos, de pacientes-moradores sem nenhum tipo de documentação, número de funcionários inferior à metade do que era determinado pela legislação federal, situação jurídica civil dos pacientes (curadores vinculados a administração do próprio hospital), denúncias de familiares, pacientes e ex-funcionários sobre maus tratos, tortura, violação de direitos, fiscalizações e divulgação na mídia, culminaram na elaboração e assinatura do Termo de Ajustamento de Conduta (TAC), em dezembro de 2012 (GARCIA, 2012; SÃO PAULO, 2012). O TAC firmado entre a União, Estado de São Paulo, Ministério Público e Prefeituras de cidades pertencentes ao DRS-XVI (Sorocaba, Piedade e Salto de Pirapora), que ainda possuíam hospitais psiquiátricos com pacientes internados, teve como objetivo a adequação da assistência aos pacientes com transtornos mentais (SÃO PAULO, 2012).

Entre 2012 e 2018, os sete hospitais da região foram fechados e os dispositivos da Rede de Atenção Psicossocial (RAPS) foram significativamente ampliados. Atualmente, a DRS-XVI apresenta cerca de 43 Centros de Atenção Psicossocial (CAPS) e 101 residências terapêuticas com 806 moradores.

Apesar do avanço, o processo de desinstitucionalização está em fase de consolidação e as mudanças são complexas. É importante que haja um programa de

suporte adequado e monitoramento contínuo dos casos, de acordo com o contexto local. Várias Leis e Portarias relacionadas ao cuidado do paciente com transtorno mental já foram publicadas, porém alguns princípios-chaves encontram-se comprometidos.

Descrição do problema:

A Organização Mundial da Saúde estima que uma em cada dez pessoas no mundo sofre de algum tipo de transtorno mental (WHO, 2014). No Brasil, os transtornos mentais afetam 20-56% da população adulta (SANTOS; SIQUEIRA, 2010).

Pesquisas mostram que a maioria dos pacientes desinstitucionalizados é capaz de viver em comunidade com um programa de suporte adequado, demonstrando melhora da função social, da autonomia, dos sintomas psiquiátricos e da qualidade de vida (ZIGURAS; STUART, 2000).

No entanto, a rápida redução dos leitos hospitalares psiquiátricos não foi acompanhada por significativa implantação de cuidados efetivos em nível comunitário (JORGE; FRANCA, 2001; SILVA et al., 2017). O êxito neste processo não é linear e não ocorreu da mesma forma em todas as regiões brasileiras. Na região de Sorocaba, onde o número de pacientes internados em leitos hospitalares era muito elevado, o processo de desinstitucionalização ultrapassou a capacidade de assimilação dos serviços ambulatoriais ofertados, fato que fragiliza a RAPS e a implementação de políticas de saúde (VIDAL; BANDEIRA; GONTIJO, 2008).

A desinstitucionalização vai além da desospitalização e da transinstitucionalização, envolve a transformação de paradigmas da sociedade em uma visão antimanicomial (OLIVEIRA; CONCIANI, 2008). A simples transferência dos pacientes de um lugar para o outro representa negligência social com suas profundas repercussões à comunidade.

O Brasil vem expandindo os modelos comunitários de atenção para pessoas com transtornos mentais, mostrando avanços e consolidação de alguns dispositivos: CAPS, Serviço Residencial Terapêutico e “Programa De Volta Para Casa” (SAÚDE MENTAL..., 2015). Mas, alguns princípios-chave preconizados pela Organização Mundial da Saúde ainda se encontram comprometidos e parecem compor o problema central: financiamento insuficiente, necessidade qualitativa e quantitativa de recursos

humanos, precariedade na estrutura física e nos insumos de serviços comunitários, carência de recursos políticos, falta de acompanhamento intensivo dos pacientes, ausência de integração entre os serviços e frágil mobilização social (WHO, 2014)**.** Esses fatores, detectados previamente em alguns estudos, prejudicam o processo de reinserção social dos pacientes desinstitucionalizados.

Pessoas com transtornos mentais requerem suporte contínuo por tempo indeterminado. Portanto, a construção de uma RAPS diversificada precisa estar fortemente alicerçada para sustentar o novo modelo de atenção e para que o modelo manicomial não seja repetido em uma versão maquiada.

Opções para abordar o problema:

Foram identificadas 5 opções para política, informadas por evidências, que podem melhorar o cuidado de pacientes com transtornos mentais desinstitucionalizados na dimensão técnico-assistencial:

Opção 1 – Disponibilizar Programas de Psicoeducação

A Psicoeducação envolve uma combinação de técnicas motivacionais, educativas, comportamentais e cognitivo-comportamentais com foco no conhecimento e compreensão sobre a doença, os sintomas, o tratamento, o prognóstico e a reabilitação (XIA; MERINDER; BELGAMWAR, 2011). Promove a educação de pacientes, familiares/cuidadores, a fim de ajudá-los a gerenciar a própria recuperação, os sintomas, o cuidado e seu tratamento, reduzindo assim a probabilidade de recaídas e hospitalizações (ZHAO et al., 2015).

Opção 2 – Implementar e monitorar a prática do Gerenciamento Intensivo de Casos

É um modelo flexível de prestação de serviços em saúde mental, caracterizado pelo manejo de casos e acompanhamento intensivo de pacientes na comunidade. Disponível 24 horas/dia, o acompanhamento é realizado por equipe multidisciplinar e direcionado a um pequeno grupo de pacientes, visando melhorar a reinserção social, o funcionamento psicossocial, o desenvolvimento da autonomia, além de promover diminuição das taxas de hospitalizações e de abandono de tratamento (DIETERICH et al., 2017).

Opção 3 – Implantar Equipes Comunitárias de Saúde Mental

Equipes multidisciplinares que oferecem cuidados especializados em saúde mental aos pacientes com transtornos mentais na comunidade, possibilitando intervenções precoces, menor taxa de admissões hospitalares e de suicídios (MALONE et al., 2007).

Opção 4 – Estruturar Serviços de Residências Terapêuticas

Estruturar os locais de moradia (casas) destinados a acolher os pacientes com transtornos mentais que permaneceram em internações psiquiátricas por muitos anos e atualmente são impossibilitados de retornar às suas famílias. Estas residências facilitam a inserção e o convívio social, o resgate da identidade e da autonomia, e sobretudo, proporcionam atendimento mais humanizado (LEFF et al., 2009).

Opção 5- Fortalecer dispositivos para intervenção em episódios psiquiátricos agudos

Essa intervenção visa fornecer cuidado e apoio ao paciente durante a crise, introduzindo um tratamento rápido, intensivo, efetivo, por tempo limitado, com política de alta precoce, através de uma equipe multidisciplinar, em um ambiente comunitário (MURPHY et al., 2015).

Considerações sobre a implementação das opções:

Para a implementação das opções para enfrentamento do problema, faz-se necessária a participação ativa dos diferentes sujeitos envolvidos, em especial, tomadores de decisão, profissionais da saúde, pesquisadores e sociedades civis. As opções precisam ser fisicamente disponíveis, geograficamente acessíveis, aceitáveis aos usuários, adequadas, efetivas e seguras. Se um desses níveis não estiver 100%, a cobertura e a efetividade das opções serão reduzidas (SILVA et al., 2014).

A Política de Saúde Mental não é tão abrangente e deixa os municípios de pequeno porte em posição de dependência de outros municípios com rede especializada em saúde mental. Custos, prioridades concorrentes, e falta de envolvimento sobre a Política de Saúde Mental podem ser as principais barreiras dos sistemas de saúde (SHEN et al., 2017). A falta de comunicação entre os níveis federal, estadual e municipal é outro ponto importante.

Há deficiência qualitativa e quantitativa de recursos humanos (KAKUMA et al., 2011). Os profissionais de saúde mental, muitas vezes, remetem a uma visão fragmentada acerca do cuidado, com vestígios de práticas manicomiais nos serviços, falta de envolvimento profissional-paciente e dificuldades de trabalhar de modo multidisciplinar (ANJOS et al., 2013).

Importantes obstáculos advindos da psicofobia, discriminação e estigmatização no que tange o imaginário social acerca da “loucura”, provocam exclusão social e isolamento, impedindo, sobretudo, a reinserção social dos pacientes desinstitucionalizados (WHO, 2001).

Faz-se necessário, providenciar constantes intervenções que disseminem conhecimento e contato social com os pacientes portadores de transtornos mentais, a fim de reduzir o estigma e os estereótipos negativos (MORGAN et al., 2018). Promover aproximação entre os gestores, profissionais de ponta e até mesmo pacientes, com o propósito de incluir as necessidades para implantação das opções no planejamento da Secretaria de Saúde e de buscar parcerias na comunidade e universidades (ANDRADE et al., 2012). Ofertar e garantir capacitação específica e educação permanente aos trabalhadores de saúde mental, assim como programas de suporte a esses profissionais (KAKUMA et al., 2011). As equipes devem ser constantemente avaliadas e monitoradas, por meio de um instrumento específico e de auditorias anuais, a fim de assegurar a efetividade da equipe e os desfechos positivos na condução dos casos (WOODY et al., 2018).

A política deve ser inteiramente implementada, aprimorada e adequada, conforme contexto da região envolvida. A formação e capacitação das equipes multidisciplinares, a qualificação da assistência prestada, bem como a infraestrutura prevista devem estar atuando de forma integrada, estruturada e organizada.

REFERÊNCIAS

ANDRADE, L. M. B. et al. Análise da implantação dos Núcleos de Apoio à Saúde da Família no interior de Santa Catarina. Saúde & Transformação Social, Florianópolis, v. 3, n. 1, p. 18-31, 2012.

ANJOS, K. F. et al. Perspectivas e desafios do núcleo de apoio à saúde da família quanto às práticas em saúde. Saúde em Debate, Rio de Janeiro, v. 37, n. 99, p. 672-680, out./dez. 2013.

BRASIL. Lei n° 10.216, de 6 de abril de 2001. Dispõe sobre a proteção e os direitos das pessoas portadoras de transtornos mentais e redireciona o modelo assistencial em saúde mental. Brasília, DF: Presidência da República, 2001. Disponível em: http://www.planalto.gov. br/ccivil_03/leis/leis_2001/l10216.htm. Acesso em: 2 abr. 2020.

BRASIL. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégicas. Reforma psiquiátrica e política de saúde mental no Brasil. Conferência regional de reforma dos serviços de saúde mental: 15 anos depois de Caracas. Brasília, DF: OPAS, 2005. Disponível em: http://bvsms. saude.gov.br/bvs/publicacoes/Relatorio15_anos_Caracas.pdf. Acesso em: 2 abr. 2020.

CAYRES, A. Z. F. et al. Caminhos para a desinstitucionalização no estado de São Paulo: censo psicossocial 2014. São Paulo: FUNDAP, 2015.

DIETERICH, M. et al. Intensive case management for severe mental illness. The Cochrane Database of Systematic Reviews, [s. l.], v. 1, Jan. 2017. CD007906.

GARCIA, M. R. V. A mortalidade nos manicômios da região de Sorocaba e a possibilidade da investigação de violações de direitos humanos no campo da saúde mental por meio do acesso aos bancos de dados públicos. Revista Psicologia Política, São Paulo, v. 12, n. 23, p. 105-120, jan. 2012.

JORGE, M. R.; FRANCA, J. M. F. A Associação Brasileira de Psiquiatria e a reforma da assistência psiquiátrica no Brasil. Revista Brasileira de Psiquiatria, São Paulo, v. 23, n. 1, p. 3-6, 2001.

KAKUMA, R., MINAS, H., VAN GINNEKEN, N., DAL POZ, M.R., DESIRAJU, K., MORRIS, J.E., SAXENA, S., SCHEFFLER, R.M. Human resources for mental health care: current situation and strategies for action. Lancet, v. 378**,** p. 1654-1663, 2011.

LEFF, H. S. et al. Does one size fit all? What we can and can't learn from a meta-analysis of housing models for persons with mental illness. Psychiatric Services, Washington, D.C., v. 60, n. 4, p. 473-482, 2009.

MALONE, D. et al. Community mental health teams for people with severe mental illnesses and disordered personality. The Cochrane Database of Systematic Reviews, [s. l.], v. 3, July 2007. CD000270.

MORGAN, A.J., REAVLEY, N.J., ROSS, A., TOO, L.S., JORM, A.F. Interventions to reduce stigma towards people with severe mental illness: Systematic review and meta-analysis. J Psychiatr Res, v. 103**,** p. 120-133, 2018.

MURPHY, S. M. et al. Crisis intervention for people with severe mental illnesses. The Cochrane Database of Systematic Reviews, [s. l.], v. 12, May 2015. CD001087.

OLIVEIRA, A. G. B. de; CONCIANI, M. E. Serviços residenciais terapêuticos: novos desafios para a organização das práticas de saúde mental em Cuiabá-MT. Revista

Eletrônica de Enfermagem, Goiânia, v. 10, n. 1, p. 167-178, 2008. Disponível em: http://www.fen.ufg.br/ revista/v10/n1/v10n1a15.htm. Acesso em: 9 ago. 2018.

SANTOS, É. G.; SIQUEIRA, M. M. Prevalência dos transtornos mentais na população adulta brasileira: uma revisão sistemática de 1997 a 2009. Jornal Brasileiro de Psiquiatria, Rio de Janeiro, v. 59, n. 3, p. 238-246, 2010.

SÃO PAULO (Estado). Ministério Público. MP e governos firmam TAC para garantir tratamento adequado a pacientes psiquiátricos da região de Sorocaba. São Paulo: MPSP, 2012. Disponível em: http://www.mpsp.mp.br/portal/page/portal/noticias/publicacao_ noticias/2012/dezembro_2012. Acesso em: 3 abr. 2020.

SAÚDE MENTAL EM DADOS. Brasília, DF: MS, ano 10, n. 12, out. 2015. Disponível em: http:// www.mhinnovation.net/sites/default/files/downloads/innovation/reports/Report_12-edicao-doSaude-Mental-em-Dados.pdf. Acesso em: 6 jan. 2017.

SHEN, G.C., EATON, J., SNOWDEN, L.R. Mainstreaming Mental Health Care in 42 Countries. Health Syst Reform, v. 3**,** p. 313-324, 2017.

SILVA, M. J. de et al. Estimating the coverage of mental health programmes: a systematic review. International Journal of Epidemiology, Oxford, v. 43, n. 2, p. 341-353, 2014.

SILVA, P. R. F. et al. Desinstitucionalização de pacientes de longa permanência de um hospital psiquiátrico no Rio de Janeiro. Ciência & Saúde Coletiva, Rio de Janeiro, v. 22, n. 7, p. 2341-2352, 2017.

VIDAL, C. E. L.; BANDEIRA, M.; GONTIJO, E. D. Reforma psiquiátrica e serviços residenciais terapêuticos. Jornal Brasileiro de Psiquiatria, Rio de Janeiro, v. 57, n. 1, p. 70-79, 2008.

XIA, J.; MERINDER, L. B.; BELGAMWAR, M. R. Psychoeducation for schizophrenia. The Cochrane Database of Systematic Reviews, [s. l.], v. 6, June 2011. CD002831. Disponível em: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4170907/. Acesso em: 3 abr. 2020.

ZHAO, S. et al. Psychoeducation (brief) for people with serious mental illness. The Cochrane Database of Systematic Reviews, [s. l.], v. 4, Apr. 2015. CD010823.

ZIGURAS, S. J.; STUART, G. W. A meta-analysis of the effectiveness of mental health case management over 20 years. Psychiatric Services, Washington, D.C., v. 51, n. 11, p. 1410- 1421, Nov. 2000.

WHO. World Health Organization. World Health Report 2001. Mental health: new understanding, new hope. WHO: Geneva, Switzerland; 2001. Disponível em: https://www.who.int/whr/2001/en/whr01_en.pdf?ua=1. Acesso em: 10 set 2018.

WHO. World Health Organization. Innovation in deinstitutionalization: a WHO expert survey. Geneva: WHO, 2014.

WOODY, C.A., BAXTER, A.J., HARRIS, M.G., SISKIND, D.J., WHITEFORD, H.A. Identifying characteristics and practices of multidisciplinary team reviews for patients with severe mental illness: a systematic review. Australas Psychiatry, v. 26**,** p. 267-275, 2018.

5.1.2 Artigo científico 1 - *Knowledge translation for improving the care of deinstitutionalized people with severe mental illness in health policy*

O artigo científico ***"Knowledge translation for improving the care of deinstitutionalized people with severe mental illness in health policy"*** teve como objetivo investigar a influência das ferramentas de tradução do conhecimento na melhoria dos cuidados de pacientes com transtornos mentais desinstitucionalizados e descrever as principais deliberações e contribuições obtidas no diálogo deliberativo realizado no dia 26 de junho de 2018.

A formatação seguiu as normas da revista *Frontiers in Pharmacology* e foi publicado em 21 de janeiro de 2020.

DOI: 10.3389/fphar.2019.01470
Data da publicação: 21/01/2020
Revista: *Frontiers in Pharmacology*
ISSN: 1663-9812
Versão online: 1663-981
Fator de impacto: 4,2
Classificação Webqualis/Capes, área de Farmácia, 2020: A1

Comprovante de publicação do artigo científico encontra-se no **Anexo C.**

Knowledge translation for improving the care of deinstitutionalized people with severe mental illness in health policy

Izabela Fulone[1]; Jorge Otavio Maia Barreto[2]; Silvio Barberato-Filho[1]; Marcel Henrique de Carvalho[3]; Luciane Cruz Lopes[1*];

[1]Pharmaceutical Sciences Graduate Course, University of Sorocaba, UNISO, Brazil

[2] FIOCRUZ/EVIPNET, Brasília, Brazil

[3] Veredas Institute, Brasília, Brazil

*** Correspondence:**

Luciane Cruz Lopes (corresponding author)

E-mail: luciane.lopes@prof.uniso.br; luslopesbr@gmail.com

University of Sorocaba

Rodovia Raposo Tavares, KM 92,5 - Sorocaba, São Paulo, Brazil

ZIP Code: 18023-000

Phone: 55 19 99781-8441 Fax: 55 15 2101-7074

Keywords: evidence-informed policy; knowledge translation; health policy; policy-making; deinstitutionalisation; mental health;

Disclosure: No conflict of interest

Financial support: Fapesp grants 2017/20668-7 and EVIPNet Brazil / Ministry of Health SCON2017-02502.

Word count: 4869

Number of references: 41

Number of figures: 1

Number of tables: 3

Additional file: 4

ABSTRACT

Background: Knowledge Translation (KT) is an effective strategy that uses the best available research evidence to bring stakeholders together to develop solutions and improve public health policy-making. Despite progress, the process of deinstitutionalisation in Brazil is still undergoing consolidation, and the changes and challenges that are involved in this process are complex and necessitate evidence-informed decision-making. Accordingly, this study used KT tools to support efforts that aim to improve the care that is available to deinstitutionalised people with severe mental disorders in Brazil.

Methods: We used the Supporting Policy relevant Reviews and Trials (SUPPORT) Tools for evidence-informed health Policymaking (STP) and followed eight steps: 1) capacity building; 2) identification of a priority policy issue within a Brazilian public health system; 3) meetings with policy-makers, researchers and stakeholders; 4) development of an evidence brief (EB) that addresses the problem of deinstitutionalisation; 5) facilitating policy dialogue (PD); 6) the evaluation of the EB and PD; 7) post-dialogue mini-interviews; and 8) dissemination of the findings.

Results: Capacity building and meetings with key informants promoted awareness about the gap between research and practice. Local findings were used to define the problem and develop the EB. Twenty-four individuals (policy-makers, stakeholders, researchers, representatives of the civil society and public defence) participated in the PD. They received the EB to subsidise their deliberations during the PD, which in turn were used to validate and improve the EB. The PD achieved the objective of promoting an exhaustive discussion about the problem and proposed options and improved communication and interaction among those who are involved in mental health care. The features of both the EB and PD were considered to be favourable and helpful.

Conclusions: The KT strategy helped participants understand different perspectives and values, the interpersonal tensions that exist among those who are involved in the field of mental health, and the strategies that can bridge the gap between research and policy-making. The present findings suggest that policy dialogues can influence practice by promoting greater engagement among stakeholders who formulate or revise mental health policies.

Keywords: evidence-informed policy; knowledge translation; health policy; policy-making; deinstitutionalisation; mental health;

BACKGROUND

Knowledge translation (KT) is a dynamic and interactive process that uses evidence to make decisions and take actions that can improve health outcomes and reduce health inequities, particularly in low- and middle-income countries (LMICs) (Boyko et al., 2012).

Overall, there are different complexities and barriers that impede the application of KT for public health action in LMICs: deficits in knowledge production, the application of the available knowledge, and the use of strategies that are based on the best available evidence (Malla et al., 2018). When resources are scarce and there are strong sociocultural interferences, the translation and dissemination of knowledge can be adversely affected by contextual and local limiting factors (Newlin Meredith; Webber, 2015).

In order to promote the appropriate use of scientific evidence in the development and implementation of public health policies, KT platforms such as the Evidence-informed Policy Network (EVIPNet), which is supported by the World Health Organization (WHO), have been established to support health policy-making in Africa, Asia, and the Americas (Moat et al., 2014). The main objective of the EVIPNet is to facilitate the use of scientific knowledge in the formulation and implementation of health policies. Specifically, it focuses on the preparation of evidence briefs and policy dialogues, and adopts an approach that is similar to the Supporting Policy relevant Reviews and Trials (SUPPORT) method (Moat and Lavis, 2014).

KT platforms are change agents that have a positive impact on policy decisions, interest group interactions, and health systems (Ongolo-Zogo et al., 2018). The use of KT platforms in Uganda, Cameroon, and Lebanon demonstrate the positive impact of such platforms: the promotion of awareness, acceptance, and adoption of research-based knowledge, achievement of the health goals, reallocation of resources, and identification of the sources of conflicts (Yehia and El Jardali, 2015; Ongolo-Zogo et al., 2018).

Evidence briefs should rely on the best available systematic reviews to delineate the important aspects of the issue in question. It must integrate global evidences and local knowledge to inform deliberations about health policies among policy-makers and stakeholders (Lavis et al., 2009a). Policy dialogues use the evidence brief as primary input to subsidise the deliberations followed by the views, experiences and tacit

knowledge of different actors, who will be affect or involved by future decisions (Lavis et al., 2009b; El-Jardali et al., 2014; Yehia and El Jardali, 2015).

Since its inception in Brazil in 2007, EVIPNet has been focusing on promoting the use of scientific knowledge in the decision-making processes of the Brazilian Health System, the development of innovative strategies in health management, and the facilitation of technical cooperation regarding KT among the participant countries (EVIPNET-BRAZIL, 2019). The Brazilian network consists of the representatives of different institutions and subject-matter experts (Dias, 2014).

Accordingly, in response to the need for and challenges in the promotion of evidence-informed health policy-making in the largest city in the state of São Paulo (Sorocaba), a working group was constituted at the University of Sorocaba in 2016. This team, which consisted of researchers, doctoral students, and health professionals, was denominated as *Seriema* (Evidence Services for Monitoring & Evaluation in Health Policy).

The *Seriema* group aims to suggest and contribute to health initiatives and formulate evidence-based public policies. This group works collaboratively with the Health Department of Sorocaba, which oversees 48 additional cities in São Paulo that are together inhabited by more than three million individuals (BRAZIL, 2018).

This group seeks to design research studies in accordance with the needs of Brazilian policy-makers specially supporting deinstitutionalisation in Brazil (mainly in region of Sorocaba).

Mental health in the region of Sorocaba

In the 1980s, the history of Brazilian mental health was marked by serious denunciations of mistreatment, lack of hygiene and care for patients with mental disorders who lived in psychiatric hospitals, mainly in the region of Sorocaba (SP), Rio de Janeiro (RJ), and Barbacena (MG) (Vidal et al., 2008; Emerich, 2016). Social and political mobilizations that advocated for psychiatric reform and the approval of Federal law no. 10216 in 2001 accelerated the process of deinstitutionalisation. It also led to the understanding that hospitalisation must be the last treatment option for patients with mental disorders. Consequently, the right to receive community care services was promulgated (BRAZIL, 2001; Silva and Rosa, 2014).

Sorocaba has a population of approximately 671,186 inhabitants and a high Human Development Index (HDI = 0.8), and its economy is based on industries and commerce (BRAZIL, 2019). The city has an adequate health-care infrastructure, and its hospitals provide services to the (almost three million) inhabitants of the tertiary care level of 48 municipalities in southwest São Paulo (BRAZIL, 2018). These municipalities are smaller than Sorocaba, their economies are diversified, and their HDI ranges from 0.6 to 0.8 (BRAZIL, 2019). Mental healthcare services are not available in all 48 municipalities. Therefore, these municipalities belong to a network of mental healthcare institutions that are connected at the primary, secondary, and tertiary level (BRAZIL, 2019).

The Sorocaba region housed the largest mental asylum in the country (i.e. high number of psychiatric beds) (Cayres, 2015). The seven asylums in this region were among the ten largest Brazilian asylums that had the highest mortality rate between 2004 and 2011. Most of these deaths were due to an unknown cause, and they were especially common during the colder months of the year; the age of the youngest patient who died under these circumstances was approximately 53 years (Garcia, 2012; Cayres, 2015). In addition, there was a high number of resident patients who did not have the requisite civil documentation, and the number of mental health professionals was less than half of the number that was specified by the federal legislation (Garcia, 2012; Emerich, 2016).

During the second half of the 1990s, there were 72514 psychiatric beds in the Brazilian public health sector. In Brazil, the number of beds had reduced to 52962 in 2001; in 2014, there were 25988 psychiatric beds across the 167 psychiatric hospitals that were located in the 116 municipalities of the 23 states (BRAZIL, 2005; BRAZIL, 2015a). In 2014, the Psychosocial Census of the State of São Paulo identified 53 psychiatric hospitals across 39 municipalities, seven of which were located within the Sorocaba region and together housed 2273 patients (Cayres, 2015).

On the basis of the aforementioned census data, the federal, state, and municipal bodies signed an agreement that they would ensure the gradual deinstitutionalisation of patients with mental disorders and the closure of the seven asylums in the region (BRAZIL, 2012). However, the deinstitutionalisation process did not proceed in the same manner across the different regions of Brazil. Specifically, in regions where the number of patients that were admitted to the hospitals was very high, the institutions were underequipped to provide ambulatories and community

services. This demonstrated the insufficiency and fragility of the services that were available to meet the demands of the patients (Vidal et al., 2008). However, a few community mental health care services (e.g., Psychosocial Care Center, Therapeutic Residential Service, and the Back Home Federal Program) have been found to be effective (BRAZIL, 2015). Nevertheless, some of the key principles that have been recommended by the WHO are not adhered to, primarily due to the following reasons: insufficient funding, qualitative and quantitative human resource deficiency, poor infrastructure, a lack of political resources and intensive follow-up care, the absence of an integration between services and fragile social mobilisation (WHO, 2014; BRAZIL, 2015).

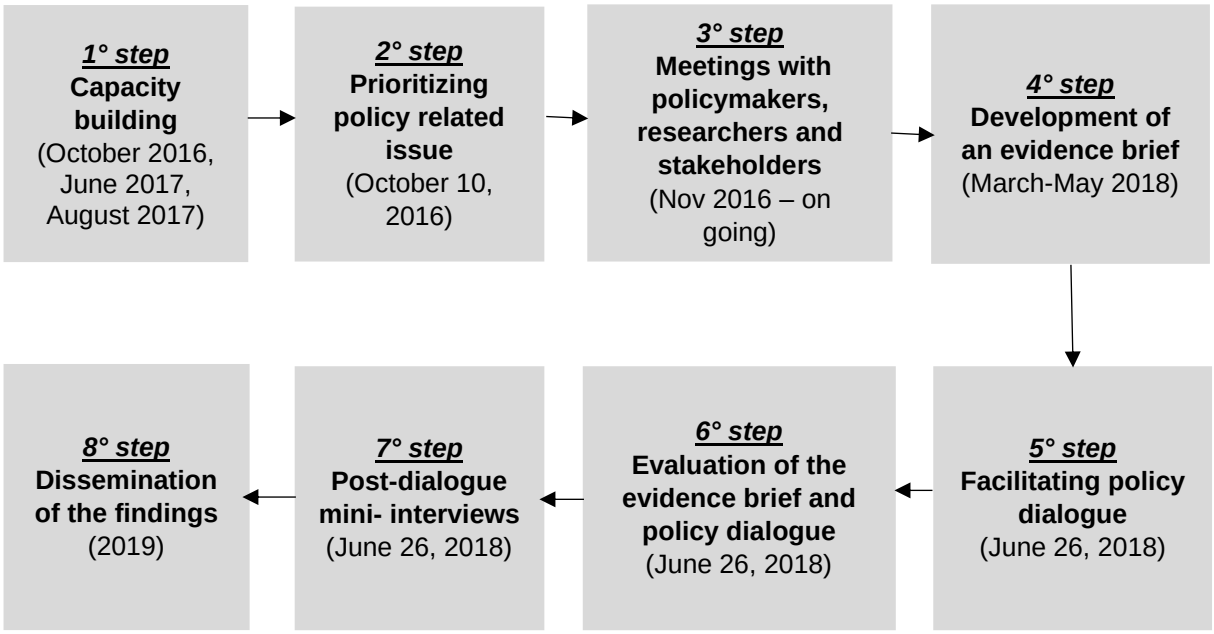
In October 2016, the Seriema organised the first workshop on evidence-based health policy during which the deinstitutionalisation of patients with mental disorders was ascribed the highest priority among all other health policy-related issues. Subsequently, the State Health Department of the Sorocaba region contacted the Seriema group with the objective of signing a partnership and helping them formulate public policies that are related to deinstitutionalisation. This represented an important opportunity to subsidise the policy and collaborate with the State Health Department. This allowed them to adapt their actions and strategies to improve the care of deinstitutionalised individuals with mental disorders in Sorocaba and the neighbouring regions.

Since the use of KT is one of the challenges that is currently faced by the health systems in LMICs, the present study investigated the means by which the care of deinstitutionalised individuals with severe mental disorders can be enhanced using KT tools.

METHODS

We used the SUPPORT Tools (Lavis et al., 2009a; Lavis et al., 2009b) for evidence-informed health Policymaking, which includes the following eight steps **(Figure 1)** for KT:

Figure 1 -Eight steps used on KT*.



*adapted from Yehia; El Jardali (Yehia and El Jardali, 2015)

1) Capacity building

There was a need to conduct capacity building workshops that addressed evidence-informed policy-making and provided technical training on the use of SUPPORT tools for relevant stakeholders. Therefore, in 2016 and 2017, three workshops were conducted to provide training and raise awareness. In addition, there was the possibility of addressing topics of interest.

2) Prioritizing and supporting evidence-informed policy-making

The first step was to prioritise policy-related issues. The Seriema group provided a set of criteria that were to be used to select important topics, and it included questions about public perceptions and the impact of the problem **(see Supplementary Materials – Table S1).**

In the first workshop, 40 participants fulfilled the criteria and they discussed their most pressing issues. Deinstitutionalisation was identified as the most important health policy-related issue by the workshop participants. With regard to the means by which the care of deinstitutionalised people with severe mental disorders can be improved,

the participants underscored the need for further evidence and to address policy-related challenges at both the national and regional levels. The chronology of events that have led to the current state of the mental health care systems in Brazil can be summarised as follows: (i) asylums provided inadequate services to their patients with mental disorders; (ii) there was immense pressure to shut down the 7 psychiatric hospitals in the region; and (iii) important changes have been made to Brazilian mental health policies.

3) Meetings with policy-makers researchers and stakeholders

A number of meetings were organised with policy-makers and stakeholders to clarify and define the problem, gather information about the status quo that could promote dialogue, and identify other key informants who could provide further insights.

4) The development of a policy brief that addresses the problem of deinstitutionalisation

Once the issue of deinstitutionalisation was prioritised, the focus was geared towards gathering a wide range of evidence on the various aspects of the issue. Therefore, a systematic review of literature was undertaken. First, a well-defined search strategy was used to retrieve relevant research articles from research databases. The search focused elements for policies that were related to the care of deinstitutionalised patients with mental disorders **(see Supplementary Materials Data Sheet 1).**

Between March and May 2018, we prepared a policy brief, which defined the problem and five evidence-based options to address the issue of deinstitutionalisation. The evidence was contextualised to the Brazilian scenario, based on the recommendations of the policy-makers, subject-matter experts, and experts in the field of mental health.

5) Facilitating policy dialogue

The policy brief was circulated to the participants 30 days prior to the dialogue to inform them of the deliberations of the meeting. A group of 24 individuals, which entailed an equal representation of policy-makers, health-care providers, researchers, and representatives of the community and public defence sectors, participated in the policy dialogue **(see Table 1)**.

Table 1: A profile of the stakeholders who participated in the policy dialogue.

Stakeholder category	N = 24 (100%)
Policy-makers[a]	5 (20.8%)
Health-care providers[b]	11 (45.8%)
Researchers in the field of public and mental health[c]	6 (25%)
Civil society organisation[d]	1 (4.2%)
Public defence representative[e]	1 (4.2%)

[a] Policy-makers at the federal, state, and municipal level; [b]Healthcare providers included mental health specialists, public health specialists, psychologists, psychiatrists, occupational therapists, nurses, and social workers; [c]Researchers from Brazilian public and private universities, EVIPNet-Brazil members, and Seriema members; [d]The Brazilian *anti-asylum* movement; [e]Public defence representative from the state of São Paulo who was involved in mental health-related legislations.

The dialogue was conducted in accordance with the method that has been described by the SUPPORT tools and Chatham House rules. It was intended to achieve the following: participant commitment and transparency, an appropriate duration of dialogue, adequate group size and representation of the participants, skilful facilitation of problem-focused discussions (i.e., five options to address the policy issue), equity, key implementation considerations, and role distribution.

6) The evaluation of the evidence brief and policy dialogue

The evaluation of the evidence brief and the policy dialogue was based on an adapted version of Lavis (2009) (Lavis et al., 2009a; Lavis et al., 2009b). Specifically, two surveys were administered to the participants (i.e., prior to dialogue and during the dialogue for those who did not complete it the first time). It consisted of items that required the respondent to assess the evidence brief and indicate the extent to which the policy dialogue was helpful on a rating scale that ranged from 1 (very unhelpful) to 7 (very helpful).

7) Post-dialogue mini-interviews

During the policy dialogue, the stakeholders were invited to participate in a video-recorded interview. In this interview, they were required to describe the insights that they gained from the dialogue. For this purpose, we posed the following two questions: a) How did the policy dialogue change your perspective about the problem in question? and b) What actions should be taken to address the problem in question?

8) Dissemination of the findings

The evidence brief was uploaded to the EVIPNet-Brazil secretariat webpage (http://brasil.evipnet.org/), where it is currently available for free download by all who are interested. A summary of the evidence brief and the policy dialogue will also be made available. Further, the federal government will order 100 prints of the evidence brief.

RESULTS

The results that are presented in the following sections summarise the main findings that pertain to the evidence brief; this section is followed by a discussion of the results that belong to the policy dialogue.

Defining the problem

What are the most important challenges that impede the improvement of mental health care that is available to deinstitutionalised people with severe mental disorders in Brazil?

The participants reviewed the findings that were presented in the evidence brief, highlighted what is already known about the problem, and provided an enriching analysis of the brief; this process consumed the most time. They individually and collectively focused on the prominent challenges: (i) insufficient and fragile community care services to meet patient needs; (ii) unequal access to community care across the different regions of Brazil; (iii) insufficient funding and a lack of political resources; (iv) qualitative and quantitative human resource deficiencies; (v) a lack of intensive follow-up care; and (vi) the absence of integration and communication between services.

All the participants agreed that it is necessary to expand and strengthen community care services for all Brazilians. Indeed, the process of deinstitutionalisation did not progress in the same manner across different Brazilian regions. In some of them, such as region of Sorocaba (main manicomial pole), where the number of patients admitted to hospital beds was very high, the deinstitutionalisation process exceeded the capacity of assimilation of services offered in community.

Some participants observed that, despite progress, community care services are still precarious with regard to a wide range of issues (i.e., from physical

infrastructure to human resources). They noted that many professionals still retain an ‘asylum mentality’, and that there is insufficient communication among mental health professionals and services, and between the municipal, state, and federal governmental bodies. The participants contended that the lack of communication and continued education adversely affects the follow-up care and rehabilitation of patients with mental disorders.

The participants expressed their concerns about the *process of* deinstitutionalisation (i.e., the withdrawal of patients from psychiatric hospitals) and trans-institutionalisation (i.e., the transfer of patients from asylums to other inappropriate institutions). Indeed, these can lead to social neglect and have profound repercussions for the community, such as increased rates of homelessness, incarceration, drug addiction (primarily, cocaine), depression, suicide, and an overloading of emergency services. All participants agreed that deinstitutionalisation requires efforts that extend beyond deinstitutionalisation and trans-institutionalisation. They also agreed that the ‘Ministry of Health must have a serious commitment to those patients who leave the psychiatric hospitals.

The participants contended that the issue of deinstitutionalisation is also complicated by financial conflicts of interests that pertain to psychiatric hospitalisations. This suggests that there is a ‘mercantilization of life of an especially vulnerable population’. Finally, the participants also recognised that the health care that is available to deinstitutionalised individuals has significantly advanced across the years; however, the socio-cultural treatment of these individuals remains problematic.

Options to address the problem of deinstitutionalisation

The five mutually non-exclusive options to address the problem of deinstitutionalisation that was articulated in the evidence brief are presented in **Table 2**.

Table 2: The definitions of the options to address deinstitutionalisation that were presented in the evidence brief.

Option	Definition
Option 1: Expand and improve the implementation of a Psychiatric Day Hospital	It is a hospital unit that offers intensive care to patients with acute mental disorders based on a multidisciplinary approach and early discharge policy (Marshall et al., 2011).
Option 2: Provide Psychoeducational programs	Psychoeducation provides patients and their families or caregivers with information about the disease, its treatment, and its prognosis (Xia et al., 2011; Zhao et al., 2015).
Option 3: Develop community mental health teams	Multidisciplinary teams provide specialised mental health care to patients with mental disorders in the community, facilitate early intervention, and lower the rates of hospital admissions and suicides (Malone et al., 2007).
Option 4: Implement and monitor the practice of intensive case management	It is a flexible model of mental health services that is characterised by intensive case management and patient care that is provided to individuals with mental disorders in the community. It is available throughout the day, and the follow-up care is provided by a multidisciplinary team to a small group of patients. They aim to improve social reintegration, psychosocial functioning, and autonomy development, and decrease the rate of hospitalisation and treatment abandonment (Dieterich et al., 2010).
Option 5: Promote assisted living	Structuring housing intended to accommodate patients with mental disorders who have been hospitalised in psychiatric institutions for many years, and are currently homeless and unable to return to their families (Leff et al., 2009).

The deliberations that pertained to the options are summarised in the following sections.

Option 1: Expand and improve the implementation of a Psychiatric Hospital Day

This option caused much polemic and controversy among the participants of the policy dialogue, possibly because of a misunderstanding of the option. A majority of the participants opposed this option because they considered traditional psychiatric hospitals to be regressive: *'something that did not work in the past, which isolates and excludes'*. At the same time that the policy dialogue was conducted, the national policy on mental health was being reformulated with a strong aim to reopen the psychiatric hospitals; evidently, many of the participants were aware of this. However, other participants understood this option more accurately and were in favour of such an

approach because it entails the early discharge policy of psychiatric day hospitals. However, they suggested that the name of the option be changed to ‘Strengthening interventions for acute psychiatric episodes’ in order to convey that this option endorses institutions that provide humane treatment to individuals who present with acute psychiatric episodes, and hospitalise briefly such individuals only when necessary.

Option 2: Provide psychoeducational programs

This option was wholeheartedly supported and endorsed by the participants. Further, a majority of the studies that were reviewed supported the effectiveness of this option. The Brazilian Health System does not offer psychoeducational programs. According to some of the participants, this may have been attributable to the preconceived notions that managers hold about mental health professionals. They also recommended the implementation of a few psychoeducational techniques.

Option 3: Develop community mental health teams

Only one of the systematic reviews (Malone et al., 2007) addressed this option. Nevertheless, the conclusions of the review suggested that this option promotes greater acceptance of the treatment and greater patient satisfaction, when compared to standard treatment paradigms. In addition, the hospitalisation rate was significantly lower; this suggests that the number of suicides and deaths under suspicious circumstances was also lower. The participants considered this option to be interesting and promising. However, the Brazilian mental health policy does not have provisions for such community mental health teams. Although Brazil does have other community teams, they comply with only a few of the principles of the proposed team.

Option 4: Implement and monitor the practice of intensive case management

Model that is similar to those of intensive case management are practiced in some communities in Brazil. Every participant considered this model to be extremely important to all Brazilian cities. However, several small towns do not comply with this model. Therefore, the participants highlighted the importance of expanding and strengthening this model.

Option 5: Promote assisted living

The participants underscored the importance of and challenges that are involved in implementing assisted living in such a manner that it does not result in trans-institutionalization.

Two participants observed issues that pertained to the inadequacy of housing, infrastructure, and food, and the absence of leisure-time activities.

Many participants agreed that cohabitating a space with individuals who differ in age, diagnosis, and the severity of the diagnosis facilitates social reintegration: ‘caring and helping each other are positive factors observed in their daily lives’.

The evidence brief and policy dialogue: Evaluation results

Eight and nine individuals out of the 24 participants completed the evaluation surveys for the evidence brief and policy dialogue, respectively. The response rate was low despite repeated attempts to administer the survey, and it can be attributed to time limitations and the busy lives that the participants led.

Despite the low response rate, the average item scores were positive, and they ranged from 5.0 to 7.0 for the evidence brief evaluation survey. The features that received the highest ranking (i.e., very helpful) were as follows: employ a graded-entry format and use systematic and transparent methods to identify, select, and assess synthesised research evidence **(see Supplementary Materials – Table S2)**.

The results of the policy dialogue evaluation were also positive, and the scores ranged from 4.6 to 6.6. The following features were considered to be very useful: rely on a facilitator to assist with the deliberation, address high-priority policy issues, do not aim for consensus, provide an exhaustive discussion, and ensure a fair representation of those who will be involved in or affected by future decisions that are related to the respective issue **(see Additional file 4)**.

Post-dialogue mini-interviews

Approximately 10 individuals agreed to participate in the post-dialogue mini-interviews, which were video-recorded. The findings of the study suggest that many participants demonstrated the positive insights that they gained during the policy dialogue **(see Table 3)**.

Table 3: Participant opinions (insights) about the policy dialogue.

'Very important space to discuss and align the thoughts so that the actions are more articulated'
'Moment of interaction between different visions and access to information that goes well beyond global evidence... greatly influenced by different views and experiences'
'It is extremely important that managers, members of civil society and academia come together to discuss mental health issues. Articulation between Ministry of Health, universities and various actors involved in mental health policy will contribute to the advancement of public health policies in mental health'
'The opportunity to listen to people who work in different areas of mental health was very important to understand better the problem and to contextualize the policy brief developed'
'Policy dialogue is very interesting because it is not a debate; people dialogue and reflect to evolve in a particular concept or a specific implementation policy... it allows the communication between the services of several levels'
'Opportunity to bring together research and management… the research shows the theoretical component that management does not have'
'An important approach between research and practice...does not seek a consensus, seeks a listening...'
'It provides an expanded view of how deep the needs are around psychiatric reform in Brazil, and how divergent the opinions are from collecting local evidence from different actors in society (local, federal, professional, and civil society managers)... representing an environment of democratic discussion'
'Listening to the most diverse opinions on the same subject, same problem... there are several actors involved and each one with a participation, experience and a point of view... very important this exchange, because it is very difficult to see from another prism'

DISCUSSION

Main findings

The application of KT tools to support efforts to improve the care of deinstitutionalised patients with mental disorders and to contribute to the promulgation of evidence-informed mental health policies was a promising and innovative experience in Sorocaba. This experience entailed eight steps, and it demonstrated to policy-makers that the process of KT can bridge the gap between research and practice.

The application of evidence in mental health practice and the exchange of knowledge between health-care providers, researchers, and community representatives were positively appraised. The entire process also helped those who are likely to be involved in or be affected by future policy-related decisions gain valuable insights. The features of the evidence brief and policy dialogue were

considered to be very helpful, and they believed that it promoted an exhaustive discussion about the issue of deinstitutionalisation.

A comparison of the present and past findings

Capacity building, which was the first step of the process, made the participants aware of the importance of the following: using KT tools to make evidence-informed policy decisions, align research at the University of Sorocaba with policy priorities, and build partnerships between policy-makers, stakeholders, and researchers. Training workshops have been found to improve knowledge and comprehension about the use of evidence in policy decision making in other countries as well (Uneke et al., 2012; Waqa et al., 2013; El-Jardali et al., 2014). The workshops also strengthened partnerships and enhanced the interaction between the Seriema group and the Health Departments of Sorocaba and the neighbouring regions.

The evidence brief was prepared based on the best evidence available on the issue at hand. However, a majority of the systematic reviews focused on high-income countries (e.g., the United States of America, the United Kingdom, Canada, Australia), and none of them were conducted in Brazil. This demonstrated a knowledge gap regarding mental health care in Brazil (Amaral et al., 2018; Votruba et al., 2018). This led to many difficulties because the relationship between evidence and policy-making depends on country-specific features (e.g., social, organisational, and public factors), the specific policy issue, resources allocation, and contextual factors, which are very different (and in some cases, deficient) in LMICs (Tricco et al., 2013; Votruba et al., 2018). This difference can be attributed to the following features that characterise LMICs: low research capacity, an obscure policy-making process, a high risk of political instability, limited financial resources, a lack of interaction between researchers and policy-makers, and lack of empowerment of civil society (Young, 2005).

Furthermore, our findings corroborate the gap between research and practice that has been observed in LMICs, as well as the difficulties and complexities that mental health care entails. Despite the global burden of mental disorders (e.g., disability and lower disability-adjusted life years), mental health is not a policy priority in LMICs (Patel, 2007; Votruba et al., 2018). Mental health policy issues differ from other policy issues because they pertain to a highly heterogeneous set of conditions (i.e., mental, behavioural, or neurodevelopmental disorders), the presence of

comorbidities, a lack of consensus on the best possible approach to treatment and care, a high rate of untreated patients, and the incumbent stigma (Votruba et al., 2018).

The definition of the problem and the options were discussed exhaustively, without the aim of reaching a consensus. The problem was perceived to be critical, and many of the participants (policy-makers, health-care providers, researchers, and representative of civil society and public defence) conceptualised the problem based on their rich practical experience, and they echoed a majority of the challenges that were already presented in the evidence brief. In other words, the policy dialogue deliberations validate the evidence brief (Yehia and El Jardali, 2015). Thus, it is noteworthy that option 2 (*Provide psychoeducational programs*) was strongly supported by findings as well as the participants. On the other hand, option 1 (*Expand and improve the implementation of a Psychiatric Day Hospital*) was strongly opposed by a majority of the participants due to local findings; further, there were differences of opinion between international and local researches. Many of the participants were aware of the grave and inhumane treatment that patients with mental disorders had been subjected to in psychiatric hospitals in this region; they were also cognisant of the struggles that were required to shut down all the hospitals. The regulation of care with regard to crisis management and the treatment of acute episodes appear to be the most unclear albeit critical aspects of mental health care in Brazil (Amaral et al., 2018).

There is no KT strategy that is singularly effective across all contexts. Therefore, it is important to report about the context-specific utility of each strategy, so that they can be modified and utilised by other interested decision makers (LaRocca et al., 2012). In this study, the participants provided positive evaluations of the evidence brief and of policy dialogue; they considered it to be favourable and useful, and these results corroborate past findings (Yehia and El Jardali, 2015; Boyko et al., 2016; Mc Sween-Cadieux et al., 2018). Similar findings emerged from the mini-interviews that were conducted at the end of the policy dialogue; specifically, all participant opinions were positive in tone. The use of a facilitator be to assist with the deliberation was considerate the most helpful feature of the policy dialogue. Past findings corroborate these results and emphasise the role of the facilitator as an unbiased agent which support KT platform (El-Jardali et al., 2014; Yehia and El Jardali, 2015).

Evidence briefs and summaries of policy dialogues (i.e., products of KT) can be used in public health policy-making only if the local and federal authorities are receptive to such efforts; unfortunately, often not the case (Cabieses and Espinoza, 2011).

Although the application of KT in public health policy-making is relatively new in LMCIs, the situation is changing. There is an increased use of evidence-informed policy frameworks (Cabieses and Espinoza, 2011; Votruba et al., 2018) and an increased demand for KT products from policy-makers. This has been proven by the EVIPNet-Brazil, which has expanded and consolidated its network (Dias, 2014). This practice needs to become a priority for Brazilian policy-makers because evidence-based public health models are powerful frameworks that can be used to identify the most effective health strategies and ensure that the resources are spent appropriately (Milat and Li, 2017).

Limitations and strengths

The present study was the first attempt to use KT tools to improve some aspects of mental health care in Brazil (e.g., deinstitutionalisation), which is a priority topic of regional and national importance. The policy dialogue brought together stakeholders who are involved in the process of deinstitutionalisation (e.g., researchers, policy-makers, health-care providers, and representatives from public defence and civil society), which enriched the deliberations and provided the participants with an opportunity to acquire new knowledge and learn from each other.

The present study has a few limitations. A large part of the KT framework and the best evidence available were developed in high-income countries (e.g., the United Kingdom, Canada, Australia) that´s can bring indirectness evidence. Further, we could not examine budgetary impact because the studies did not present cost analyses. Additionally, some of the options that were identified were difficult to understand because they were articulated using obscure terminologies. The variability in the quality of the reviewed studies and the lack of information about the options that can be implemented are a few other limitations. The low response rate that was evidenced for the evidence brief and policy dialogue evaluation surveys was attributed to time limitations and the busy lives that our participants led; therefore, some of our results may be underestimated. Although we have conducted an exhaustive and in-depth discussion, some topics that pertained to implementation were not discussed due to

the paucity of time. However, since some aspects of implementation vary across communities, they should be discussed in accordance with the conditions of each municipality.

CONCLUSIONS

The KT process that was adopted was considered to be a useful means to discuss important policy issues, bring together policy-makers, health-care providers, researchers, and representatives of civil society and public defence, enhance interaction and partnerships between evidence-producers and evidence-users, and promote the dissemination and application of global and local evidence in practice.

The present study did not seek to examine causal relationships. Nevertheless, a longer study period will allow future researchers to capture the positive changes in mental health care that result from KT. Future investigations are required to understand whether and how evidence briefs and policy dialogue can be used to improve the care of deinstitutionalised people with severe mental disorders and their contributions to Brazilian mental health policy.

Researchers and other stakeholders who are interested in using KT tools should consider the lessons that were learnt during the course of our study.

DECLARATIONS:

Ethical approval and consent to participate: not applicable. This is a documentary research, which we used administrative data.

Consent for publication: not applicable.

Availability of data and material: The data generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Conflict of Interest statement: The authors declare that they have no competing interests.

Funding: Fapesp grants 2017/20668-7 and EVIPNet Brazil / Ministry of Health SCON2017-02502.

Authors contributions statement: Luciane Cruz Lopes (LCL) conceptualized the study. Izabela Fulone (IF), Jorge Otávio Maia Barreto (JOMB) and LCL designed the study. IF, LCL, Silvio Barberato-Filho (SBF) and Marcel Henrique de Carvalho (MHC)

led data collection, carried out the analysis and drafted the initial manuscript. All authors read (IF, LCL, JOMB, SBF and MHC) provided critical revision and approved the final manuscript.

Acknowledgements: Thanks to Health Departments of Sorocaba and region.

REFERENCES

Amaral, C.E., Onocko-Campos, R., De Oliveira, P.R.S., Pereira, M.B., Ricci, E.C., Pequeno, M.L., Emerich, B., Dos Santos, R.C., and Thornicroft, G. (2018). Systematic review of pathways to mental health care in Brazil: narrative synthesis of quantitative and qualitative studies. *Int J Ment Health Syst* 12**,** 65.

Boyko, J.A., Kothari, A., and Wathen, C.N. (2016). Moving knowledge about family violence into public health policy and practice: a mixed method study of a deliberative dialogue. *Health Res Policy Syst* 14**,** 31.

Boyko, J.A., Lavis, J.N., Abelson, J., Dobbins, M., and Carter, N. (2012). Deliberative dialogues as a mechanism for knowledge translation and exchange in health systems decision-making. *Soc Sci Med* 75**,** 1938-1945.

Brazil (2001). Lei n° 10.216, de 6 de abril de 2001, que dispõe sobre a proteção e os direitos das pessoas portadoras de transtornos mentais e redireciona o modelo assistencial em saúde mental. 2001. Available at: https://hpm.org.br/wp-content/uploads/2014/09/lei-no-10.216-de-6-de-abril-de-2001.pdf (Accessed May 10 2017).

Brazil (2012). SÃO PAULO (Estado). Ministério Público. Procuradoria Geral da Justiça. Termo de Ajuste e Conduta (TAC). São Paulo, 18 de dezembro de 2012. Available at: http://pfdc.pgr.mpf.mp.br/temas-de-atuacao/saude-mental/atuacao-do-mpf/tac-desinstitucionalizacao-de-hospitais-psiquiatricos-2012 (Accessed Jul 20 2017).

Brazil (2015). Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégicas. Coordenação Geral de Saúde Mental, Álcool e Outras Drogas. Saúde Mental em Dados – 12, Ano 10, nº 12. Brasília: Informativo eletrônico de dados sobre a Política Nacional de Saúde Mental, 2015, 48p. Available at: http://www.mhinnovation.net/sites/default/files/downloads/innovation/reports/Report_12-edicao-do-Saude-Mental-em-Dados.pdf (Accessed Jan 10 2017).

Brazil (2018). São Paulo. SP Notícias. Novo Hospital Regional de Sorocaba será referência em alta complexidade. Available at: http://www.saopaulo.sp.gov.br/spnoticias/ultimas-noticias/em-sorocaba-alckmin-entrega-hospital-de-alta-complexidade-com-260-leitos/ (Accessed Jul 13 2019).

Brazil (2019). The Brazilian Institute of Geography and Statistics – IBGE. Cidades e Estados. Available at:

https://ww2.ibge.gov.br/english/disseminacao/eventos/missao/instituicao.shtm (Accessed Apr 25 2019).

Cabieses, B., and Espinoza, M.A. (2011). La investigación traslacional y su aporte para la toma de decisiones en políticas de salud. *Revista Peruana de Medicina Experimental y Salud Publica* 28**,** 288-297.

Cayres, A.Z.F.E.A. (2015). Secretaria da Saúde. Caminhos para a desinstitucionalização no estado de São Paulo: censo psicossocial 2014. São Paulo: FUNDAP, 2015. Available at: http://www.saude.sp.gov.br/resources/ses/perfil/profissional-da-saude/grupo-tecnicodeacoesestrategicasgtae/saudemental/censopsicossocial/censo_psicossocial_2014.pdf (Accessed Jun 10 2019).

Dias, R.I.D.B., Jorge Otávio Maia ; Souza, Nathan Mendes (2014). Desenvolvimento atual da Rede de Políticas Informadas por Evidências (EVIPNet Brasil): relato de caso. *Rev Panam Salud Publica* 36**,** 50-56.

Dieterich, M., Irving, C.B., Park, B., and Marshall, M. (2010). Intensive case management for severe mental illness. *Cochrane Database Syst Rev***,** Cd007906.

El-Jardali, F., Lavis, J., Moat, K., Pantoja, T., and Ataya, N. (2014). Capturing lessons learned from evidence-to-policy initiatives through structured reflection. *Health Res Policy Syst* 12**,** 2.

Emerich, B.F.Y., Silvio (2016). O hospital psiquiátrico em diálogos atemporais. *Interface* 20**,** 207-216.

Evipnet-Brazil (2019). Rede para Políticas Informadas por Evidências. Ministério da Saúde - Departamento de Ciência e Tecnologia (Decit). Available at: http://brasil.evipnet.org/sobre/ (Accessed Marc 20 2019).

Garcia, M.R.V. (2012). A mortalidade nos manicômios da região de Sorocaba e a possibilidade da investigação de violações de direitos humanos no campo da saúde mental por meio do acesso aos bancos de dados públicos. *J Revista Psicologia Política* 12**,** 105-120.

Larocca, R., Yost, J., Dobbins, M., Ciliska, D., and Butt, M. (2012). The effectiveness of knowledge translation strategies used in public health: a systematic review. *BMC Public Health* 12**,** 751.

Lavis, J.N., Boyko, J.A., Oxman, A.D., Lewin, S., and Fretheim, A. (2009b). SUPPORT Tools for evidence-informed health Policymaking (STP) 14: Organising and using policy dialogues to support evidence-informed policymaking. *Health Res Policy Syst* 7 Suppl 1**,** S14.

Lavis, J.N., Permanand, G., Oxman, A.D., Lewin, S., and Fretheim, A. (2009a). SUPPORT Tools for evidence-informed health Policymaking (STP) 13:

Preparing and using policy briefs to support evidence-informed policymaking. *Health Res Policy Syst* 7 Suppl 1**,** S13.

Leff, H.S., Chow, C.M., Pepin, R., Conley, J., Allen, I.E., and Seaman, C.A. (2009). Does one size fit all? What we can and can't learn from a meta-analysis of housing models for persons with mental illness. *Psychiatr Serv* 60**,** 473-482.

Malla, C., Aylward, P., and Ward, P. (2018). Knowledge translation for public health in low- and middle- income countries: a critical interpretive synthesis. *Glob Health Res Policy* 3**,** 29.

Malone, D., Newron-Howes, G., Simmonds, S., Marriot, S., and Tyrer, P. (2007). Community mental health teams (CMHTs) for people with severe mental illnesses and disordered personality. *Cochrane Database Syst Rev***,** Cd000270.

Marshall, M., Crowther, R., Sledge, W.H., Rathbone, J., and Soares-Weiser, K. (2011). Day hospital versus admission for acute psychiatric disorders. *Cochrane Database Syst Rev***,** Cd004026.

Mc Sween-Cadieux, E., Dagenais, C., and Ridde, V. (2018). A deliberative dialogue as a knowledge translation strategy on road traffic injuries in Burkina Faso: a mixed-method evaluation. *Health Res Policy Syst* 16**,** 113.

Milat, A.J., and Li, B. (2017). Narrative review of frameworks for translating research evidence into policy and practice. *Public Health Res Pract* 27.

Moat, K.A., and Lavis, J.N. (2014). Suporte para uso de evidências de pesquisa nas Américas através do "one-stop shop" eletrônico: EVIPNet. *Cadernos de Saúde Pública* 30**,** 2697-2701.

Moat, K.A., Lavis, J.N., Clancy, S.J., El-Jardali, F., and Pantoja, T. (2014). Evidence briefs and deliberative dialogues: perceptions and intentions to act on what was learnt. *Bull World Health Organ* 92**,** 20-28.

Newlin Meredith; Webber, M. (2015). Effectiveness of knowledge translation of social interventions across economic boundaries: a systematic review. *European Journal of Social work* 18**,** 543-568.

Ongolo-Zogo, P., Lavis, J.N., Tomson, G., and Sewankambo, N.K. (2018). Assessing the influence of knowledge translation platforms on health system policy processes to achieve the health millennium development goals in Cameroon and Uganda: a comparative case study. *Health Policy Plan* 33**,** 539-554.

Patel, V. (2007). Mental health in low- and middle-income countries. *Br Med Bull* 81-82**,** 81-96.

Silva, E.K.B.D., and Rosa, L.C.D.S. (2014). Desinstitucionalização Psiquiátrica no Brasil: riscos de desresponsabilização do Estado. *Revista Katálysis* 17**,** 252-260.

Tricco, A.C., Cogo, E., Ashoor, H., Perrier, L., Mckibbon, K.A., Grimshaw, J.M., and Straus, S.E. (2013). Sustainability of knowledge translation interventions in healthcare decision-making: protocol for a scoping review. *BMJ Open* 3.

Uneke, C.J., Ezeoha, A.E., Ndukwe, C.D., Oyibo, P.G., and Onwe, F. (2012). Promotion of evidence-informed health policymaking in Nigeria: bridging the gap between researchers and policymakers. *Glob Public Health* 7**,** 750-765.

Vidal, C.E.L., Bandeira, M., and Gontijo, E.D. (2008). Reforma psiquiátrica e serviços residenciais terapêuticos. *Jornal Brasileiro de Psiquiatria* 57**,** 70-79.

Votruba, N., Ziemann, A., Grant, J., and Thornicroft, G. (2018). A systematic review of frameworks for the interrelationships of mental health evidence and policy in low- and middle-income countries. *Health Res Policy Syst* 16**,** 85.

Waqa, G., Mavoa, H., Snowdon, W., Moodie, M., Nadakuitavuki, R., Mc Cabe, M., and Swinburn, B. (2013). Participants' perceptions of a knowledge-brokering strategy to facilitate evidence-informed policy-making in Fiji. *BMC Public Health* 13**,** 725.

WHO (2014). World Health Organization and the Gulbenkian Global Mental Health Plataform. Innovation in deinstitutionalization: a WHO expert survey. Geneva: World Health Organization, 2014.

Xia, J., Merinder, L.B., and Belgamwar, M.R. (2011). Psychoeducation for schizophrenia. *Cochrane Database Syst Rev***,** Cd002831.

Yehia, F., and El Jardali, F. (2015). Applying knowledge translation tools to inform policy: the case of mental health in Lebanon. *Health Res Policy Syst* 13**,** 29.

Young, J. (2005). Research, policy and practice: why developing countries are different. *Journal of International Development* 17**,** 727–734.

Zhao, S., Sampson, S., Xia, J., and Jayaram, M.B. (2015). Psychoeducation (brief) for people with serious mental illness. *Cochrane Database Syst Rev***,** Cd010823.

THE IDENTIFICATION AND PRIORITIZATION OF THEMES

(Supplementary Material – Table S1)

Table S1: Specify, in a few words, the problem that you would like to work with SERIEMA group:

About your initial perception of the problem		Comments
a) Is it a prevalent health problem in the population?	▪Yes ▪ No	
b) Does the problem jeopardize service delivery or local health policy?	▪ Yes ▪ No	
c) Are there local policies or guidelines on the problem?	▪ Yes ▪ No	
c) Are there local policies or guidelines on the problem?	▪ Yes ▪ No	
e) Does the problem induce unnecessary costs to the Brazilian Health System?	▪ Yes ▪ No	
f) Are the team and decision makers willing to solve the problem?	▪ Yes ▪ No	

We will select criteria to prioritize the problems to be addressed within SERIEMA group. We will use the form below to identify the most important criteria. Consider the scale below:

- 1 points out the unimportant criteria;
- 5 indicate the most important criteria.
- Then evaluate how the problem highlighted above relates to the corresponding criteria.
- In this case, the scale will start at 1 (no impact of the problem on the criteria) up to 5 (high impact of the problem on the criteria).

Criteria	Criteria weight	Impact of the problem
1. Severity and prevalence of health condition	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5
2. Social cost of health status	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5
3. Potential results of evidence synthesis to improve outcome/benefit to health	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5
4. Potential results of the synthesis of evidence to change costs for the health system	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5
5. Potential results of the synthesis of evidence to contribute to the improvement of quality of care	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5
6. Potential results of evidence synthesis in reducing health risks	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5
7. Unit or aggregate cost of the problem	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5
8. Sufficient availability of scientific evidence	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5
9. Controversy or great interest among health professionals	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5
10. Requirements of State actions	■ 1 ■ 2 ■ 3 ■ 4 ■ 5	■ 1 ■ 2 ■ 3 ■ 4 ■ 5

Please register your name and email to resolve any questions:

Specify, in a few words, another problem that you would like to work with SERIEMA group:

Systematic Search for the development of an evidence brief to address the problem of deinstitutionalisation

Supplementary material - Data Sheet 1

Once the issue of deinstitutionalisation was prioritised, the focus was geared towards gathering a wide range of evidence relevant on the various aspects of the issue. Firstly, a systematic search was conducted using the following research databases: *Virtual Health Library, The Cochrane Library, PubMed, Health Evidence, Rx for Change, The Cumulative Index to Nursing and Allied Health Literature (CINAHL), Excerpta Medica Database (EMBASE), American Psychological Association (PsycINFO), Epistemonikos, Latin American & Caribbean Health Sciences Literature (LILACS), the Health System Performance Index (IDSUS), the Strategic Management Support Room (SAGE), and the National Collection of Health Resources of the Department of Informatics of the Brazilian Unified Health System (COLECIONASUS)*. We used a well-defined search strategy, and we did not place restrictions based on the language or date of publication.

The retrieval of articles was conducted using a combination of the following terms: *'Deinstitutionalization', 'Mental Disorders', 'Community Mental Health Services', 'Case Management', 'Managed Care Programs', 'Community Mental Health Centres', 'Supported Housing', 'Psychoeducation', 'Community Mental Health Team', 'Crisis Intervention'.* These terms were used irrespective of whether they were indexed in the Medical Subject Headings (MeSH) System. We also manually searched the reference lists and citations of secondary studies to identify eligible studies.

Subsequently, we selected articles that pertained to the policies that are related to the care of deinstitutionalised patients with mental disorders. The quality of the systematic reviews was assessed using the measurement tool for the 'Assessing the Methodological Quality of Systematic Reviews'(AMSTAR 1).

The evidence brief evaluation survey items

(Supplementary Material – Table S2)

Table S2: The evidence brief evaluation survey items.

Questions pertaining to design features	Mean n=8
Described the relevant context and different characteristics of the problem	6.5
Described some options to address the problem	6.5
Described key implementation considerations of the options	6.5
Quality considerations when discussing the research evidence	6.5
Local applicability considerations when discussing the research evidence	5.0
Equity considerations into when discussing the research evidence	6.0
Evidence brief employed a graded-entry format	7.0
Evidence brief reviewed for both scientific quality and system relevance	6.0
Evidence brief employed systematic and transparent methods to identify, select and assess synthesised research evidence	7.0

[a]The questions were adapted from Lavis et al. (25).
[b]The response scale ranged from 1 (very unhelpful) to 7 (very helpful).

The policy dialogue evaluation survey items

(Supplementary Materials – Table S3)

Table S3: The policy dialogue evaluation survey items.

Questions pertaining to design features[a]	Mean[b] n=9
Addressed high-priority policy issues	6.6
Provided an opportunity to discuss different aspects of the issues	6.4
Provided an opportunity to discuss possible options for addressing issues	5.7
Provided an opportunity to discuss key implementation considerations	4.7
Provided an opportunity to discuss who might do what differently	5.8
Deliberative was informed by a pre-circulated issue brief	6.1
Included discussion about factors that can inform how to approach the issues, possible options for addressing them and key implementation considerations	6.3
Ensured fair representation among those who will be involved or affected by future decisions related to the issue	6.5
Engaged a facilitator to assist with the deliberation	6.7
Allowed for frank, off-the-record deliberations following the Chatham House Rule	6.2
Did not aim for consensus	6.4
Reached the goal of promoting an exhaustive discussion	6.5

[a] The questions were adapted from Lavis et al.[8] and Boyko et al[37].
[b] The response scale ranged from 1 (very unhelpful) to 7 (very helpful).

5.1.3 Artigo científico 2 - *Improving care for deinstitutionalized people with mental disorders: experiences of the use of knowledge translation tools*

Este artigo científico teve como objetivo identificar intervenções efetivas, baseadas nas melhores evidências científicas disponíveis, para melhorar o cuidado de pacientes com transtornos mentais desinstitucionalizados. O mesmo referiu-se a uma atualização do livro da síntese publicado em 2020 (ISBN: 978-85-334-2769-3). Neste artigo, a atualização da busca em bases de dados científicas (13/01/2020) identificou novos estudos gerando mais uma opção/estratégia para o cuidado dessa população.

A formatação seguiu as normas da revista *Frontiers in Psychiatric.* Foi submetido em 22 de junho de 2020 e encontra-se em fase de revisão.

Revista: *Frontiers in Psychiatric*
ISSN: 1664-0640
Versão online: 1664-0640
Fator de impacto: 2,84
Classificação Webqualis/Capes, área de Farmácia, 2020: A3

Comprovante de submissão do artigo encontra-se no **Anexo D.**

IMPROVING CARE FOR DEINSTITUTIONALIZED PEOPLE WITH MENTAL DISORDERS: EXPERIENCES OF THE USE OF KNOWLEDGE TRANSLATION TOOLS

Izabela Fulone[1], Jorge Otavio Maia Barreto[2], Silvio Barberato-Filho[1], Cristiane Bergamaschi[1], Marcus Tolentino Silva[1], Luciane Cruz Lopes[1*]

[1] Pharmaceutical Sciences Graduate Course, University of Sorocaba, UNISO, Sorocaba, Brazil

[2] Fiocruz School of Government, Fiocruz Brasília, Oswaldo Cruz Foundation, Brasília, Brazil

***Corresponding author: Luciane Cruz Lopes**
Pharmaceutical Sciences Graduate Course, University of Sorocaba, UNISO, Sorocaba, Brazil
Rodovia Raposo Tavares, KM 92,5 - Sorocaba, São Paulo, Brazil 23
ZIP Code: 18023-000 24
Phone: 55 19 99781-8441 Fax: 55 15 2101-7074
E-mail: luciane.lopes@prof.uniso.br; luslopesbr@gmail.com

Disclosure: No conflict of interest.
Financial support: Fapesp grants 2017/20668-7 and EVIPNet Brazil / Ministry of Health SCON2017-02502
Word count:4188
Number of references: 44
Number of figures: 3
Number of tables: 1
Supplementary materials: 5

ABSTRACT

Background: The deinstitutionalization process is complex, long-term and many countries fail to achieve progress and consolidation. Informing decision-makers about appropriate strategies and changes in mental health policies can be a key factor for it. This study aimed to develop an evidence brief to summarize the best available evidence to improve care for deinstitutionalized patients with severe mental disorders in the community.

Methods: We used the SUPPORT (Supporting Policy Relevant Reviews and Trials) tools to elaborate the evidence brief and to organize a policy dialogue with 24 stakeholders. A systematic search was performed in 10 electronic databases and the methodological quality of systematic reviews (SRs) was assessed by AMSTAR 2.

Results: Fifteen SRs were included (comprising 378 studies and 69,736 participants), of varying methodological quality (3 high-quality SRs, 2 moderate-quality SRs, 7 low-quality SRs, 3 critically low SRs). Six strategies were identified: i. Psychoeducation; ii. Anti-stigma programs, iii. Intensive case management; iv. Community mental health teams; v. Assisted living; and vi. Interventions for acute psychiatric episodes. They were associated with improvements on a global status, satisfaction with the service, reduction on relapse, and hospitalization. Challenges to implementation of any of them included: stigma, the shortage of specialized human resources, limited political and budgetary support.

Conclusions: These strategies could guide future actions and policymaking to improve mental health outcomes.

Key-words: evidence-informed policy; knowledge translation; deinstitutionalization, mental health; community mental health services;

BACKGROUND

Deinstitutionalization is the procedure of shifting the care and support from long-stay psychiatric hospitals to community mental health services for patients diagnosed with severe mental disorders (Fakhoury and Priebe, 2007). This procedure works in two ways. The first concentrates on reducing the population size of mental institutions. The second emphasizes reforming psychiatric care and developing special services to reduce dependence, isolation and other behaviours that make it difficult for patients to adjust to life outside of care (Lamb and Bachrach, 2001).

Deinstitutionalization emerged in the post-World War II period in the 1950s in the US and the UK due to several factors, such as poor and inhumane living conditions, human rights violations, harmful treatment practices, the introduction of more effective psychotropic drugs and the high cost of mental hospitals (Taylor Salisbury et al., 2016). Although many countries have advanced and reached positive levels in this process, such as USA, England, Italy, Germany and UK, others are still starting the process and are facing many problems (Taylor Salisbury et al., 2017). Many challenges remain in low-and middle-income countries, Eastern Europe, and Eastern and Southeastern Asian countries (Kunitoh, 2013; Krupchanka and Winkler, 2016)

This complex process entails ensuring access to and developing special alternative community services for the care of the physical and mental health of the mentally ill, non-institutionalized population, with the aim to improve quality of life, ensure citizenship and promote social inclusion (Lamb and Bachrach, 2001; Razzouk, 2019).

Many countries fail because they close institutions without careful planning and without implementing community (WHO, 2007). Failures to establish basic infrastructure, to diversity and to integrate the mental health services are the most common (Akiyama et al., 2008). This fact can have serious effects such as homelessness, marginalization, and 'reinstitutionalization' or 'transinstitutionalization' into prisons or asylums as well as worsening psychiatric conditions and crowding emergency department (Winkler et al., 2016).

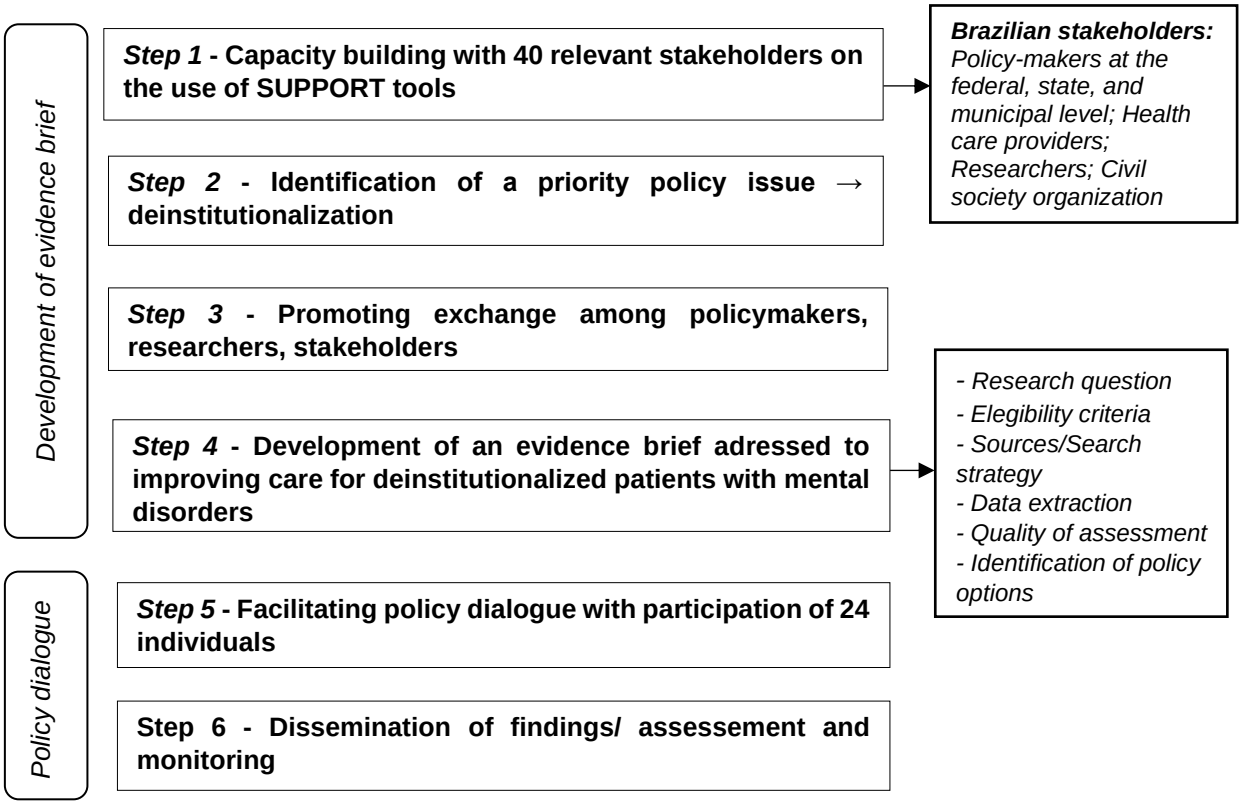
Informing decision makers about positive strategies and appropriate changes in mental health policies could be a key factor for mental healthcare development (Winkler et al., 2016; Bhugra et al., 2018). Considering Brazil, as a case scenario, this study aimed to identify effective strategies to improve care for deinstitutionalized

patients with mental disorders in the community, through the use of knowledge translation tools.

METHOD

The SUPporting POlicy relevant Reviews and Trials (SUPPORT) tools (Lavis et al., 2009a;Lavis et al., 2009b) were used to guide the process as methods to obtain evidence to inform health policymaking and to develop an evidence brief and to organize the policy dialogue, **Figure 1**.

Figure 1 - Steps used on elaboration of evidence brief.



Eligibility criteria of the studies

Inclusion criteria

Participants: patients 18 years of age and older suffering from severe and persistent non-affective mental disorders (schizophrenia and schizophreniform, schizoaffective

or schizotypal disorders or multiple diagnoses) who were or not institutionalized in psychiatric hospitals.

Interventions: strategies for outpatient follow-up and care in the community.

Comparator: comparison with usual/standard care, other strategies for outpatient follow-up and care in the community or nothing.

Outcome: compliance with medication, relapse, satisfaction with the service, internalized stigma reduction, reduction in stigmatizing attitudes, hospitalization, contacts with mental health services, improve of the global and mental state, social rehabilitation status, quality of life, death by suicide, stability, equity, harms and costs.

Timing: any duration of follow-up.

Studies design: systematic reviews (SR), overview of SRs and economic assessment studies. We selected these study designs because they are at the top of the hierarchy of evidence pyramid.

Exclusion criteria

We excluded articles that evaluated only the clinical outcomes related to psychiatric patients without providing information regarding management strategies, actions and/or methodologies for the process of monitoring deinstitutionalized patients, as well as outdated SRs whose topics have been addressed in updated SRs. Studies that reported results only for patients with mild mental disorders or with dementia or intellectual disorders or substance abuse or for people with mental disorders who were already living on the street (homeless) were excluded.

Sources of information and search strategy

The electronic search of eligible studies was performed in the following databases until 13 January 2020: Virtual Health Library, Cochrane Library, PubMed, Health Evidence, Rx for Change, Cumulative Index to Nursing and Allied Health Literature, Excerpta Medica Database, American Psychological Association, Epistemonikos, Latin American & Caribbean Health Sciences Literature.

We also screened the reference lists of secondary studies and manually searched for references in journals and databases. We did not apply any limits on language or date of publication. The search strategy in Medline (Ovid) is presented in **Supplementary Material – Data Sheet 1**. We adapted it to each database.

Study selection process and data extraction

Two review authors (IF, CB) independently screened the titles and abstracts for inclusion. Then, the full texts of potentially relevant references were retrieved, and two review authors (IF, CB) independently assessed the full-text articles for inclusion and extracted all relevant data. Any disagreements were resolved by a third review author (LCL). Data extracted included the following: author, year, type and number of primary studies included, year range of the primary studies, setting of included studies, total number of subjects, type of intervention and of comparator, type of outcome measure and main outcomes.

We also checked barriers and facilitators general for implement strategies for outpatient follow-up and care in the community and their inequities. To verify inequities for implement health policies, we used the PROGRESS (place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital) framework to ensure considerations for health equity (O'Neill et al., 2014).

Quality assessment of systematic reviews

The quality of the SRs was assessed using the updated “A Measurement tool for Assessing the Methodological Quality of Systematic Reviews” (AMSTAR 2) (Shea et al., 2017).

AMSTAR 2 considers seven critical domains (items 2, 4, 7, 9, 11, 13 and 15) to rate the overall confidence in the findings of each SR.

Organization of policy dialogue

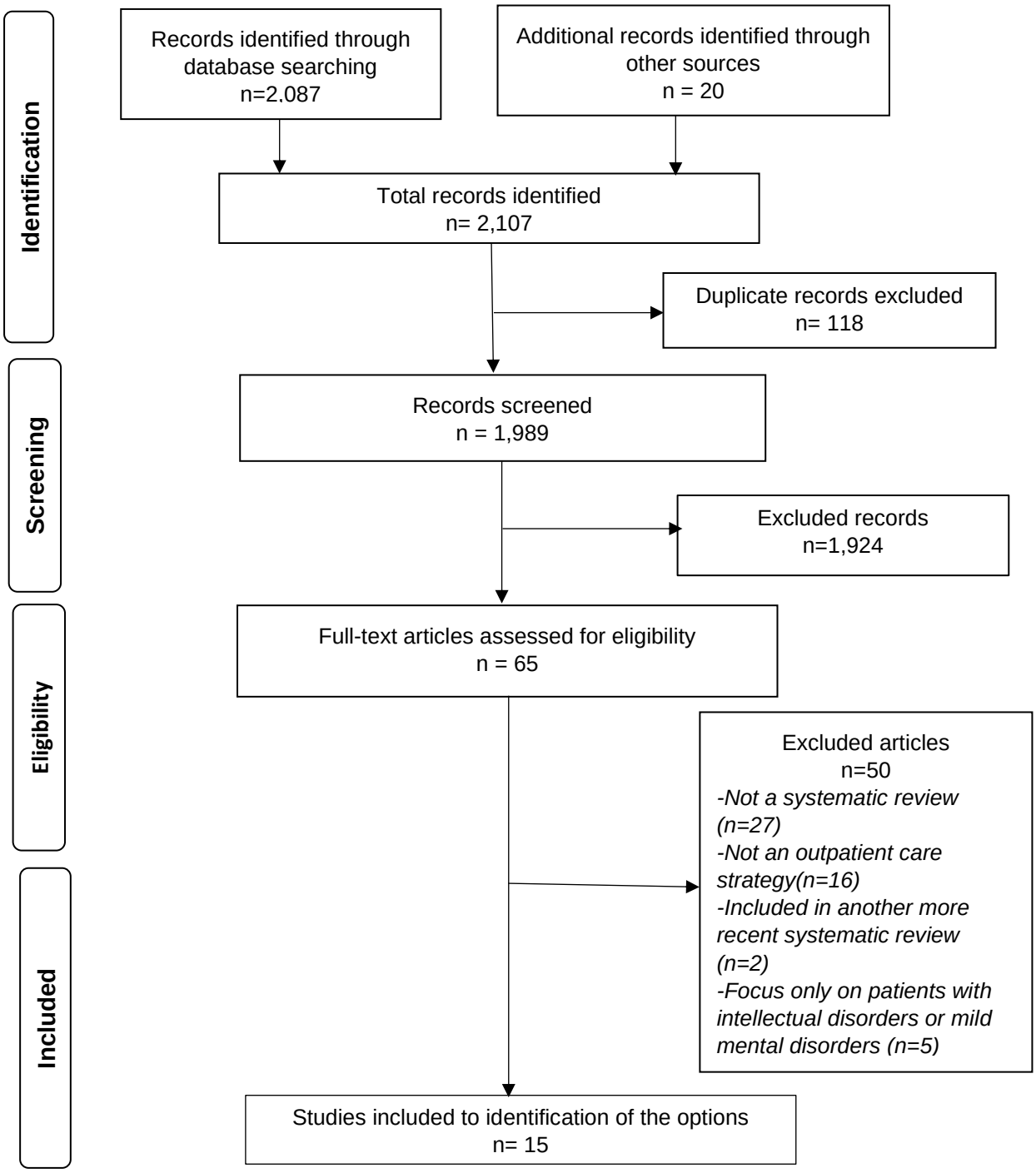
A policy dialogue was organized to discuss the evidence brief with relevant stakeholders involved in the problem. A preliminary version of the evidence brief was pre-circulated among participants and the strategies and key implementation considerations were discussed during the policy dialogue. After, the evidence brief was aligned and updated according to the deliberations and outputs produced.

RESULTS

Overall, 2,107 references were retrieved. Sixty-five studies were selected and examined in detail; fifteen SRs met the scope of this evidence brief and were selected

to develop the policy strategies (see detailed results reported in **Supplementary Material – Table S1**), while fifty studies were excluded (**see Supplementary Material – Table S2**). A flow diagram illustrates the inclusion process, **Figure 2**.

Figure 2: Flow diagram for study selection



From the 15 SRs, we identified six strategies to improve care for deinstitutionalized patients: i. psychoeducation; ii. anti-stigma programmes; iii. intensive case management; iv. community mental health teams; v. assisted living; and vi. interventions for acute psychiatric episodes. The main characteristics of the included reviews are summarized in **Table 1**.

Table 1 - Characteristics of the included systematic reviews.

Author, Year	Number of studies included	Year range of the studies	Total number of subjects	Main outcomes	Quality of assessment (AMSTAR 2)
STRATEGY 1: PSYCHOEDUCATION					
Pilling, 2002**	18	1978-1997	1,467	- relapse - readmission - death (suicide) - burden, expressed emotion - medication compliance	critically low
Lincoln, 2007**	18	1982-2005	1,534	- relapse/rehospitalization - symptoms - knowledge - functional outcome - medication adherence	Low
Xia, 2011**	44	1988-2009	5,142	- compliance with medication and follow- up - relapse - satisfaction with the service	Moderate
Zhao, 2015*	20	1988-2009	2,337	- compliance with medication and follow- up - relapse	High
STRATEGY 2: ANTI-STIGMA PROGRAMS					
Tsang, 2016**	14	2007-2015	1,131	- reduction in internalized stigma	critically low
Wood, 2016**	12	2002-2016	714	- improvement in internalized stigma	low
Xu, 2017**	17	2011-2015	2,373	- effects on perceived/ experienced/anticipated stigma - effects on self-prejudice - effects on stigma coping	critically low
Morgan, 2018**	62	2001-2017	9,002	- reductions in stigmatising attitudes - desire for social distance	low
STRATEGY 3: INTENSIVE CASE MANAGEMENT					
Burns, 2007**	29	1988-2005	1,996	- days of hospitalization	Low
Dieterich, 2010**	40	1985-2005	7,524	- hospitalization - improve of global state - reducing death by suicide - social functioning (on unemployment)	High
STRATEGY 4: COMMUNITY MENTAL HEALTH TEAMS					
Malone, 2017**	3	1992-1998	587	- death (suicide /suspicious circumstances) - hospitalization - satisfaction with the service - social functioning	moderate

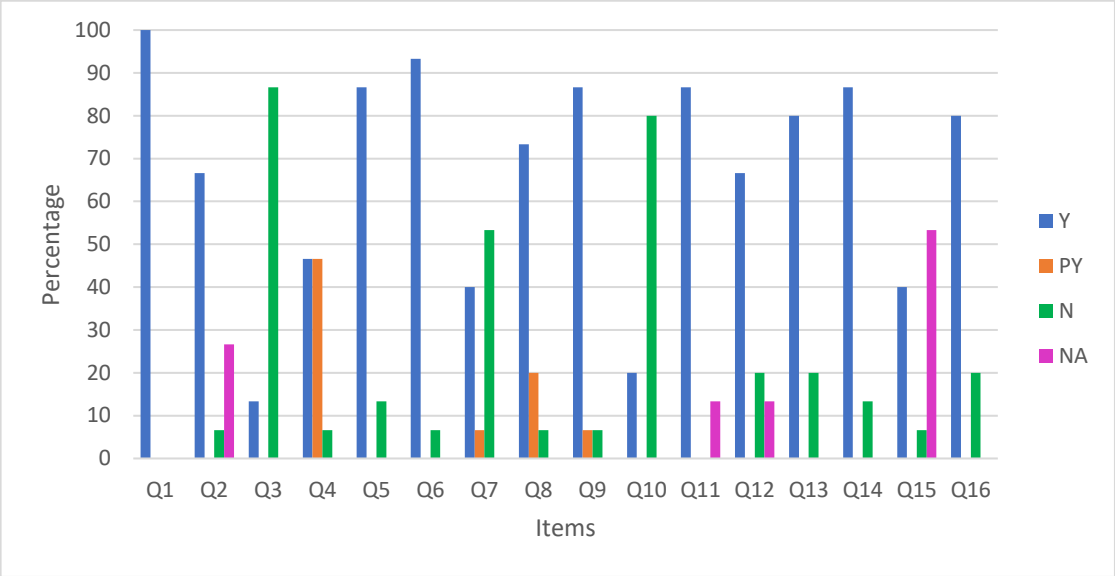
Table 1 (continuation) - Characteristics of the included systematic reviews.

Author, Year	Number of studies included	Year range of the studies	Total number of subjects	Main outcomes	Quality of assessment (AMSTAR 2)
STRATEGY 5: ASSISTED LIVING					
Leff, 2009*	44	1983-2006	13,436	- housing stability - reduction in psychiatric symptoms - reduction in hospitalization - reduction in alcohol abuse or drug abuse - increased employment - increased satisfaction	low
McPherson, 2018*	28¨	1990-2017	6,516#	- housing stability - hospitalization - symptoms of mental illness - social functioning	low
STRATEGY 6: INTERVENTIONS FOR ACUTE PSYCHIATRIC EPISODES					
Murphy, 2015**	8	1964-2010	1,144	- hospitalization - improve mental state and global state - satisfaction with the care - quality of life - burden family	High
Wheeler, 2015*	21&	1993-2011	14,833##	- hospital admissions - characteristic of service	Low

* Systematic review without meta-analysis; ** Systematic review with meta-analysis; ¨ studies included in deinstitutionalization subgroup; & studies included in the quantitative analysis; #one study did not declare total n; ## seven studies did not declare total n;

As already noted in the Table 1, three (20.0%) SRs were considered high in quality, two (13.3%) moderate, seven (46.6%) low, and three (20.0%) critically low. Weaknesses were found in items 3, 4, 7 and 10. Thirteen (86.6%) of the included SRs failed to provide justification for their selection of study designs (item 3). A comprehensive literature search strategy was revealed in seven (46.6%) of the SRs, but the remaining studies failed to do so because they did not show a justification for language restrictions or did not search for grey literature (item 4, critical domain). Eight (53.3%) of them did not provide a list of excluded studies that were read in full-text form or report reasons for their exclusion (item 7, critical domain). Twelve (80.0%) of them did not report on the sources of funding for the studies included (item 10), **Figure 3.** AMSTAR results are provided in **Supplementary Materials – Table S3**.

Figure 3 - Comparison of quality assessment of included reviews using AMSTAR 2 criteria.



Y, yes; PY, partial yes; N, no; NA, not applicable;

No potential harm or cost-effectiveness was pointed out in the SRs included. There are few cost data, and no conclusions regarding cost-effectiveness can be drawn.

Twenty-four individuals participated of policy dialogue (5 of them were policymakers, 11 health care providers, 6 researches, 1 from civil society organization and 1 representant from public defense) and discussed exhaustibly the problem, viable strategies and considerations for implementation. The process, outcomes and lessons learnt during this dialogue were showed in details in elsewhere (Fulone et al., 2019). The findings of each strategy showed in the SRs and the main contributions obtained in the policy dialogue are summarized as follow.

Strategy 1: Psychoeducation

Four SRs (Pilling et al., 2002; Lincoln et al., 2007; Xia et al., 2011; Zhao et al., 2015) addressed the effectiveness of psycho-educational programmes as a means of improving care for severely mentally ill people. This strategy received strong endorsement from all participants of the policy dialogue (Fulone et al., 2019).

Psychoeducation involves any group or individual programme with a combination of motivational, educational and behavioural techniques focused on knowledge and understanding of the disease, symptoms, treatment, prognosis and

rehabilitation, and it should be directed to the patient, caregivers and family members (Xia et al., 2011).

When this intervention is addressed to patients, it promotes greater adherence to treatment in the short, medium and long term, lower relapse rates in medium and long term and greater satisfaction with the service (Xia et al., 2011; Zhao et al., 2015).

Nevertheless, psychoeducation with families (n= 18 studies) showed more effective in reducing relapse/rehospitalization (follow-up 7-12 months) than psychoeducation without families. The effect size for knowledge was small and was no significant effect on symptoms change, functioning and medication adherence. At longer follow-up (>12 months), the results on relapse/rehospitalization also failed (Lincoln et al., 2007).

Aside from that, educational interventions offered to caregivers or families in comparison to all other treatments, standard care or other types of active treatments have shown benefits over relapse in the first twelve months, but this effect was not sustainable between 1-2 years. The single-family interventions demonstrated greater effectiveness over group family treatments to prevent readmissions in the long term (1-2 years) and to reduce the burden (Pilling et al., 2002). The both SRs (Pilling et al., 2002; Lincoln et al., 2007) suggest the additional effort to integrating families and to offering psychoeducational interventions for longer periods.

Strategy 2: Anti-stigma programs

Four SRs were addressed the reduction of stigma (Tsang et al., 2016; Wood et al., 2016; Xu et al., 2017; Morgan et al., 2018). This option came after discussions about the Psychoeducation strategy with stakeholders. As some studies showed specific results, directing psychoeducation to reduce stigma, the participants suggested separating psychoeducation strategies that focused directly on reducing stigma and those related to the education of family members or patients to learn about the disease. Thus, this strategy was added as one of the post-dialogue suggestions.

Many interventions have been developed to reduce the negative impact, the discrimination and misconceptions around the public stigma and of internalized stigma towards people with severe and persistent mental disorders (Morgan et al., 2018). The main approaches include psychoeducation, combined or not with other components, such as cognitive behavioural therapy, social skills training or group discussion elements (Tsang et al., 2016; Wood et al., 2016; Xu et al., 2017).

Some SRs (Tsang et al., 2016; Xu et al., 2017) showed that psychoeducation was effective to reduce the internalized stigma and the self-prejudice. On the other hand, a SR (n= 12 studies) involving psychoeducation and/or other of psychosocial interventions (cognitive behaviour therapy, social skills training, photovoice) did not found significant changes in internalized stigma at the end of the therapy or at follow up to 4 months (Wood et al., 2016).

To reduce the public stigma towards people with severe mental illness, education interventions, mixed or not with contact interventions, showed immediate positive effects. At the end of the treatment, stigmatizing attitudes and desire for social distance were reduced, but at follow up 6 months, the benefits were not sustainable (Morgan et al., 2018).

Strategy 3: Intensive case management

Two SRs (Burns et al., 2007; Dieterich et al., 2010) highlighted the effectiveness of the practice of intensive case management. It was considered as one of the main axes of deinstitutionalization by participants of policy dialogue (Fulone et al., 2019). This strategy is characterized by an integrated model of health care delivery and follow-up that aims to provide systematic, flexible and coordinated mental health services according to the health and social care needs of people with severe mental illness (Dieterich et al., 2010).

This intervention model decreased the number of days of hospitalization, increased the retention in care, improved global state and promoted greater patient satisfaction (Dieterich et al., 2010). Nevertheless, other studies have shown a reduction in the hospitalization rate only for patients at high risk of hospital admission, who tend to use more of these services than patients who already have low hospitalization rates (Burns et al., 2007).

Strategy 4: Community mental health teams

One SR (Malone et al., 2007) addressed the effectiveness of community mental health teams. It was considered promising strategy by participants of policy dialogue (Fulone et al., 2019). A community mental health team is a multidisciplinary team composed of specialists in mental health, who should lead and be responsible for providing expert assessment, treatment and care to the population of a given area in the community (Malone et al., 2007). These team is different of other services including

crisis intervention (24 hours' service) or assertive community treatment (restricted caseloads).

It can be a way of integrating mental health into primary care. In addition, having greater contact with patients and families makes it possible to detect and intervene earlier in some serious symptoms or other diagnoses (Simmonds et al., 2001). Community mental health team follow-up promotes greater patient satisfaction with the service, lower hospital admission rate than standard care (without community mental health teams) and improvement of social functioning including police contacts. Although the evidence is still insufficient, follow-up performed by such teams tends to reduce the number of suicides (Malone et al., 2007).

Strategy 5: Assisted living

Two SRs (Leff et al., 2009; McPherson et al., 2018) addressed the benefits of community housing models for deinstitutionalized persons with severe mental illness. Participants of policy dialogue recognized the important role of this strategy in the deinstitutionalization process and the need to ensure adequate structure and organization (Fulone et al., 2019). Post-deinstitutionalization, assisted living emerged due to the housing needs for former patients of large psychiatric hospitals who had been resettled in the community. Housing models vary in terms of their physical structure, staffing arrangements, levels of support, recovery focus, discharge and move-on policies (McPherson et al., 2018).

Patients living in residential care and treatment model housing have shown greater stability, reduction in hospitalization and in psychiatric symptoms (Leff et al., 2009).

Strategy 6: Interventions for acute psychiatric episodes

Two SRs (Murphy et al., 2015; Wheeler et al., 2015) addressed the effectiveness of models for interventions for acute psychiatric episodes. Interventions in acute psychiatric episodes should provide rapid assessment and intensive treatment for a brief period through a multidisciplinary team specialized in crisis situations either in a community setting or in the patient's own home. Such interventions represent a viable alternative that is less stigmatized than standard hospitalization (Murphy et al., 2015). This strategy was realigned post-dialogue and the prominent discussion that

emerged was related to ensure brief and intensive treatment, and to defend the end of hospitalization for long periods (Fulone et al., 2019).

Despite the results on hospitalization, improvement in mental and global status, and quality of life remains inconclusive, crisis interventions promote greater satisfaction with treatment and less burden on family compared to standard care received in a hospital (Murphy et al., 2015). In other SR (n = 21 studies), it was not feasible to summarize the data due to the variety of design of included studies, but suggest to reduce hospitalizations and highlight some key components that should be available: 24-hour service provision, including psychiatrists, high-quality staff training and integration with other local mental health services (Wheeler et al., 2015).

Implementation barriers and inequities

The planning and implementation in mental health policies should consider the characteristics of the option itself, the outer setting (social, political and economic context), the inner setting (structural characteristics, relationships) and the characteristics of the individuals involved (knowledge, skills) (Chinman et al., 2017). Some of these factors can represent barriers that are likely to be encountered at the political, professional, patient and societal levels. Some common barriers in mental health are showed in **Supplementary Material – Table S4**.

The deliberations focused mainly on the stigma, lack of funding and political will (Fulone et al., 2019). Participants emphasized that the stigma of being labelled as a deinstitutionalized patient needs to change and can no longer be considered as an unpredictable, dangerous individual, unable to live in the community. Perhaps, overcoming stigma is the biggest challenge.

Stigma, discrimination, cultural beliefs and negative societal responses to people with mental illness are recognized as one of the largest barriers in the mental health area (WHO, 2001), remaining strong in society, in patients and among health professionals. It is necessary to raise public awareness and promote education campaigns (Hailemariam et al., 2016).

Although the staff composition of health professionals varies by setting, population needs, the type of health system and the availability of financial resources, the shortage of appropriate human resources for mental health, particularly in low-middle-income countries, is recognized as a global concern (Kakuma et al., 2011; Shen et al., 2017). Establishing effective training programmes, clear documentation practices and

supervision about quality of services are strategies recommended (Kakuma et al., 2011; Woody et al., 2018).

Low political priority, insufficiency resource, knowledge-action gap in policy implementation and lack of partnership formation with other sectors are important obstacles that needs to be overcome (Shidhaye, 2015; Chinman et al., 2017; Shen et al., 2017).

Cooperation from all levels of government to implement and review mental health policy, configuration of proactive partnerships and the adoption of scientific implementation frameworks are facilitators to improve the care practice (Chinman et al., 2017; Shen et al., 2017; Bhugra et al., 2018).

Half the strategies implemented delivered effective outcomes in the replicate sites due contextual differences, inequalities and the unpredictable behaviour of the system (Shidhaye, 2015). Some groups or places may be potentially disadvantaged or under different conditions, which obscures the effectiveness of an option.

People with low socioeconomic conditions, with physical disability or frailty, and who lives in rural area were considered to be potentially disadvantaged. Poor rural people have few or no local treatment options and their access in the city is expensive. They are also less likely to achieve long term follow-up (Akiyama et al., 2008). Strategies to overcome these iniquities include integration to primary care, subsidy for treatment and facility transportation in emergency cases (Hailemariam et al., 2016). WHO recommends the integration and strength of primary healthcare to mental health services in order to decrease the global gap in mental health (Ayano, 2018).

DISCUSSION

The available evidence from 15 SRs covered six different types of strategies that can lead to meaningful improvements in care for deinstitutionalized people with mental disorders and their health outcomes. They can complement each other, but not necessarily have to be employed together. The outcomes, estimates of effects, and the quality of SRs varied. The paucity of studies and conflicting evidence has been observed in some strategies. The deliberations obtained in the policy dialogue contributed to align the strategies, to improve the evidence brief and validate it.

There was extensive evidence for the positive effects of the psychoeducation (strategy 1), but the true benefits and cost-effectiveness in the short and long-term still

are uncertain (Xia et al., 2011; Zhao et al., 2015), as well as whether it is better to apply group delivery rather than individually, or only with patients or with the family (Pilling et al., 2002; Lincoln et al., 2007). Similarly, the wide variety of combined strategies in the anti-stigma programs (strategy 2) also showed conflicting results and it was unfeasible to determine whether there is any recommendation on which strategy or duration is most effective (Tsang et al., 2016; Wood et al., 2016; Xu et al., 2017; Morgan et al., 2018).

The lack of fidelity to maintain and apply key components in the structure and organization aspect of an original model as Intensive case management (strategy 3) could explain the variation in some outcomes (e.g., hospitalization) between studies and the level of effectiveness (Burns et al., 2007; Dieterich et al., 2010). Not all studies measured fidelity adequately to the original strategy.

Despite the number of primary studies existing in some strategies such as Assisted living (strategy 5) and Interventions for acute psychiatric episodes (strategy 6), the wide variety of instruments used to measure clinical and non-clinical results, the heterogeneity of the retrieved studies designs and the definitional inconsistency makes it impossible to combine some data, which reduces the power of conclusion and the degree of evidence confidence. Two SRs were unable to summarize the data due to the heterogeneity of the recovered study designs (Wheeler et al., 2015; McPherson et al., 2018). The lack of consistency in the definition of active components or terminology used in the published literature about assisted living models (strategy 5) has limited the evidence on which model is most effective and safe (McPherson et al., 2018).

Whilst we found more studies within of some strategies, there was the strategy 3, Community mental health teams, with only a single SR, which included three trials (Malone et al., 2007). Some evidence is scarce and much more robust studies are needed.

We were unable to investigate the potential for harms associated with these strategies that might influence benefits, because any SR reported adverse events. Cost-effectiveness and consequences of implementing any of these strategies as a routine service was not assessed. Much more studies should be undertaken in this area to explore the costs, to measure the health economic outcomes and the harms of the strategies, in order to make them more attractive for managers and policymakers.

Considerations about the implementation barriers of any of the strategies are complex should be interpreted with caution. Barriers and facilities have dynamic

nature, change over time and may be more or less affected according the extern context (Lau et al., 2016).

There is a real need to support evidence-based policy making. Combining research evidence with views, experiences and tacit knowledge from relevant stakeholders is a promising strategy. Policy dialogue strengthened interactions with policy makers, stakeholders and research and raised awareness of the importance of applying evidence to policies. Positive lessons have occurred in other countries (Mulvale et al., 2014; Yehia and El Jardali, 2015) and need to be disseminated worldwide, especially in low- and middle-income countries.

STRENGTHS AND LIMITATIONS

This study evaluated a wide range of interventions and summarized in a single document the best evidence available to improve the care of patients with deinstitutionalized mental disorders in the community, including some implementation barriers, facilitators, and equity considerations. This policy brief is not restricted to only one audience, can reach mental health professionals, researchers, and policymakers and likely easier to be understood. It is also one of the few studies that reported experiences of use of knowledge translation tools combining development of an evidence brief and organization of policy dialogue in a middle-income country and addressed the issue of deinstitutionalization.

The majority of the SRs focused on high-income countries (United States of America, the United Kingdom, Canada), which revealed a gap in low-income countries. Considering Brazil as a case scenario, we could verify that although it has implemented several of these strategies, we did not find any SR including assessment of them in the Brazilian setting. There are certainly relevant primary studies that not have been included in a SR, so our results could represent only part of the evidence.

Some strategies were based on studies with low quality of evidence, limiting confidence in their findings. Some outcomes are under-researched such as cost, cost-benefit, harms, implementation barriers and equity. Further studies should be conducted in low-middle-income countries because several factors are very different and, in some cases, deficient. There is a need to know the challenges they may face and whether the results are generalizable for these contexts.

More rigorous methods are needed to improve the validity of SRs, to provide high-quality evidence, and to increase the applicability of the findings by decision-

makers. In addition, much more effects need to be explored and well-reported. Emphasis should be given to underreported outcomes, which involve patient outcomes and the advance of public health, harms, costs and inequities.

CONCLUSIONS

This evidence brief showed six strategies based on the best evidence available and considering the strengths and weaknesses of each to improve care for deinstitutionalized people with severe mental disorders. The intention is not to advocate specific strategies or to for close discussion but to inform and to promote deliberations among policymakers and stakeholders with regard to the preferred strategies and their planning of implementation according to needs, financial resources, feasibility, the local reality and engagement among key actors. Thus far, there is no consensus regarding which key components and implementation strategies are essential for successful mental health care service in the community.

DECLARATIONS:

Ethical approval and consent to participate: not applicable.

Consent for publication: not applicable

Availability of data and material: The data generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Conflict of Interest statement: The authors declare that they have no competing interests.

Funding: Fapesp grants 2017/20668-7 and EVIPNet Brazil / Ministry of Health SCON2017-02502.

Authors contributions statement: Luciane Cruz Lopes (LL) conceptualized the study. Izabela Fulone (IF), Jorge O. M. Barreto (JB) and LL designed the study. IF, LL, Silvio Barberato-Filho (SB), Cristiane Bergamaschi (CB) and Marcus Tolentino Silva (MS) participated in the study search strategy process. IF an CB participated in the study selection process and extraction of data. IF and LL assessed the quality of studies. IF and LL drafted the manuscript and all authors (IF, LL, JB, SB, CB and MS) contributed to and have approved the final manuscript.

REFERENCES

Akiyama, T., Chandra, N., Chen, C.N., Ganesan, M., Koyama, A., Kua, E.E., Lee, M.S., Lin, C.Y., Ng, C., Setoya, Y., Takeshima, T., and Zou, Y. (2008). Asian models of excellence in psychiatric care and rehabilitation. *Int Rev Psychiatry* 20**,** 445-451. doi: 10.1080/09540260802397537

Ayano, G. (2018). Significance of mental health legislation for successful primary care for mental health and community mental health services: A review. *Afr J Prim Health Care Fam Med* 10**,** e1-e4. doi: 10.4102/phcfm.v10i1.1429

Bhugra, D., Pathare, S., Joshi, R., Kalra, G., Torales, J., and Ventriglio, A. (2018). A review of mental health policies from Commonwealth countries. *Int J Soc Psychiatry* 64**,** 3-8. doi: 10.1177/0020764017745108

Burns, T., Catty, J., Dash, M., Roberts, C., Lockwood, A., and Marshall, M. (2007). Use of intensive case management to reduce time in hospital in people with severe mental illness: systematic review and meta-regression. *Bmj* 335**,** 336. doi:10.1136/bmj.39251.599259.55

Chinman, M., Woodward, E.N., Curran, G.M., and Hausmann, L.R.M. (2017). Harnessing Implementation Science to Increase the Impact of Health Equity Research. *Med Care* 55 Suppl 9 Suppl 2**,** S16-s23. doi: 10.1097/MLR.0000000000000769

Dieterich, M., Irving, C.B., Park, B., and Marshall, M. (2010). Intensive case management for severe mental illness. *Cochrane Database Syst Rev***,** Cd007906. doi: 10.1002/14651858.CD007906.pub2

Fakhoury, W., and Priebe, S. (2007). Deinstitutionalization and reinstitutionalization: major changes in the provision of mental healthcare. *Psychiatry* 6**,** 313-316.

Fulone, I., Barreto, J.O.M., Barberato-Filho, S., De Carvalho, M.H., and Lopes, L.C. (2019). Knowledge Translation for Improving the Care of Deinstitutionalized People With Severe Mental Illness in Health Policy. *Front Pharmacol* 10**,** 1470. doi: 10.3389/fphar.2019.01470

Hailemariam, M., Fekadu, A., Selamu, M., Medhin, G., Prince, M., and Hanlon, C. (2016). Equitable access to integrated primary mental healthcare for people with severe mental disorders in Ethiopia: a formative study. *Int J Equity Health* 15**,** 121. doi: 10.1186/s12939-016-0410-0

Kakuma, R., Minas, H., Van Ginneken, N., Dal Poz, M.R., Desiraju, K., Morris, J.E., Saxena, S., and Scheffler, R.M. (2011). Human resources for mental health care: current situation and strategies for action. *Lancet* 378**,** 1654-1663. doi: 10.3389/fphar.2019.01470

Krupchanka, D., and Winkler, P. (2016). State of mental healthcare systems in Eastern Europe: do we really understand what is going on? *BJPsych Int* 13**,** 96-99.

Kunitoh, N. (2013). From hospital to the community: the influence of deinstitutionalization on discharged long-stay psychiatric patients. *Psychiatry Clin Neurosci* 67**,** 384-396.

Lamb, H.R., and Bachrach, L.L. (2001). Some perspectives on deinstitutionalization. *Psychiatr Serv* 52**,** 1039-1045. doi: 10.1176/appi.ps.52.8.1039

Lau, R., Stevenson, F., Ong, B.N., Dziedzic, K., Treweek, S., Eldridge, S., Everitt, H., Kennedy, A., Qureshi, N., Rogers, A., Peacock, R., and Murray, E. (2016). Achieving change in primary care--causes of the evidence to practice gap: systematic reviews of reviews. *Implement Sci* 11**,** 40. doi: 10.1186/s13012-016-0396-4

Lavis, J.N., Boyko, J.A., Oxman, A.D., Lewin, S., and Fretheim, A. (2009b). SUPPORT Tools for evidence-informed health Policymaking (STP) 14: Organising and using policy dialogues to support evidence-informed policymaking. *Health Res Policy Syst* 7 Suppl 1**,** S14.

Lavis, J.N., Permanand, G., Oxman, A.D., Lewin, S., and Fretheim, A. (2009a). SUPPORT Tools for evidence-informed health Policymaking (STP) 13: Preparing and using policy briefs to support evidence-informed policymaking. *Health Res Policy Syst* 7 Suppl 1**,** S13. doi: 10.1186/1478-4505-7-s1-s13. doi: 10.1186/1478-4505-7-s1-s14

Leff, H.S., Chow, C.M., Pepin, R., Conley, J., Allen, I.E., and Seaman, C.A. (2009). Does one size fit all? What we can and can't learn from a meta-analysis of housing models for persons with mental illness. *Psychiatr Serv* 60**,** 473-482. doi: 10.1176/appi.ps.60.4.473

Lincoln, T.M., Wilhelm, K., and Nestoriuc, Y. (2007). Effectiveness of psychoeducation for relapse, symptoms, knowledge, adherence and functioning in psychotic disorders: a meta-analysis. *Schizophr Res* 96**,** 232-245. doi: 10.1016/j.schres.2007.07.022

Malone, D., Newron-Howes, G., Simmonds, S., Marriot, S., and Tyrer, P. (2007). Community mental health teams (CMHTs) for people with severe mental illnesses and disordered personality. *Cochrane Database Syst Rev***,** Cd000270. doi: 10.1002/14651858.CD000270.pub2

Mcpherson, P., Krotofil, J., and Killaspy, H. (2018). Mental health supported accommodation services: a systematic review of mental health and psychosocial outcomes. *BMC Psychiatry* 18**,** 128. doi: 10.1186/s12888-018-1725-8

Morgan, A.J., Reavley, N.J., Ross, A., Too, L.S., and Jorm, A.F. (2018). Interventions to reduce stigma towards people with severe mental illness: Systematic review and meta-analysis. *J Psychiatr Res* 103**,** 120-133. doi: 10.1016/j.jpsychires.2018.05.017

Mulvale, G., Chodos, H., Bartram, M., Mackinnon, M.P., and Abud, M. (2014). Engaging civil society through deliberative dialogue to create the first Mental Health Strategy for Canada: Changing Directions, Changing Lives. *Soc Sci Med* 123**,** 262-268. doi: 10.1016/j.socscimed.2014.07.029

Murphy, S.M., Irving, C.B., Adams, C.E., and Waqar, M. (2015). Crisis intervention for people with severe mental illnesses. *Cochrane Database Syst Rev***,** Cd001087. doi: 10.1002/14651858.CD001087.pub5

O'neill, J., Tabish, H., Welch, V., Petticrew, M., Pottie, K., Clarke, M., Evans, T., Pardo Pardo, J., Waters, E., White, H., and Tugwell, P. (2014). Applying an equity lens to interventions: using PROGRESS ensures consideration of socially stratifying factors to illuminate inequities in health. *J Clin Epidemiol* 67**,** 56-64. doi: 10.1016/j.jclinepi.2013.08.005

Pilling, S., Bebbington, P., Kuipers, E., Garety, P., Geddes, J., Orbach, G., and Morgan, C. (2002). Psychological treatments in schizophrenia: I. Meta-analysis of family

intervention and cognitive behaviour therapy. *Psychol Med* 32**,** 763-782. doi: 10.1016/j.jclinepi.2013.08.005

Razzouk, D. (2019). Accommodation and Health Costs of Deinstitutionalized People with Mental Illness Living in Residential Services in Brazil. *Pharmacoecon Open* 3**,** 31-42. doi: 10.1007/s41669-018-0078-z

Shea, B.J., Reeves, B.C., Wells, G., Thuku, M., Hamel, C., Moran, J., Moher, D., Tugwell, P., Welch, V., Kristjansson, E., and Henry, D.A. (2017). AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj* 358**,** j4008. doi: 10.1136/bmj.j4008

Shen, G.C., Eaton, J., and Snowden, L.R. (2017). Mainstreaming Mental Health Care in 42 Countries. *Health Syst Reform* 3**,** 313-324. doi: 10.1080/23288604.2017.1356424

Shidhaye, R. (2015). Implementation Science for closing the treatment gap for mental disorders by translating evidence base into practice: experiences from the PRIME project. *Australas Psychiatry* 23**,** 35-37. doi: 10.1177/1039856215609771

Simmonds, S., Coid, J., Joseph, P., Marriott, S., and Tyrer, P. (2001). Community mental health team management in severe mental illness: a systematic review. *Br J Psychiatry* 178**,** 497-502; discussion 503-495. doi: 10.1192/bjp.178.6.497

Taylor Salisbury, T., Killaspy, H., and King, M. (2016). An international comparison of the deinstitutionalisation of mental health care: Development and findings of the Mental Health Services Deinstitutionalisation Measure (MENDit). *BMC Psychiatry* 16**,** 54. doi: 10.1186/s12888-016-0762-4

Taylor Salisbury, T., Killaspy, H., and King, M. (2017). The relationship between deinstitutionalization and quality of care in longer-term psychiatric and social care facilities in Europe: A cross-sectional study. *Eur Psychiatry* 42**,** 95-102. doi: 10.1016/j.eurpsy.2016.11.011

Tsang, H.W., Ching, S.C., Tang, K.H., Lam, H.T., Law, P.Y., and Wan, C.N. (2016). Therapeutic intervention for internalized stigma of severe mental illness: A systematic review and meta-analysis. *Schizophr Res* 173**,** 45-53. doi: 10.1016/j.schres.2016.02.013

Wheeler, C., Lloyd-Evans, B., Churchard, A., Fitzgerald, C., Fullarton, K., Mosse, L., Paterson, B., Zugaro, C.G., and Johnson, S. (2015). Implementation of the Crisis Resolution Team model in adult mental health settings: a systematic review. *BMC Psychiatry* 15**,** 74. doi: 10.1186/s12888-015-0441-x

WHO (2001). World Health Organization. World Health Report 2001. Mental health: new understanding, new hope. Geneva: World Health Organization, 2001.

WHO (2007). World Health Organization. The optimal mix of services. Available at: https://www.who.int/mental_health/policy/services/2_Optimal%20Mix%20of%20Services_Infosheet.pdf (Accessed Ago 15 2019).

Winkler, P., Barrett, B., Mccrone, P., Csemy, L., Janouskova, M., and Hoschl, C. (2016). Deinstitutionalised patients, homelessness and imprisonment: systematic review. *Br J Psychiatry* 208**,** 421-428. doi: 10.1192/bjp.bp.114.161943

Wood, L., Byrne, R., Varese, F., and Morrison, A.P. (2016). Psychosocial interventions for internalised stigma in people with a schizophrenia-spectrum diagnosis: A systematic narrative synthesis and meta-analysis. *Schizophr Res* 176**,** 291-303. doi: 10.1016/j.schres.2016.05.001

Woody, C.A., Baxter, A.J., Harris, M.G., Siskind, D.J., and Whiteford, H.A. (2018). Identifying characteristics and practices of multidisciplinary team reviews for patients with severe mental illness: a systematic review. *Australas Psychiatry* 26**,** 267-275. doi: 10.1177/1039856217751783

Xia, J., Merinder, L.B., and Belgamwar, M.R. (2011). Psychoeducation for schizophrenia. *Cochrane Database Syst Rev***,** Cd002831. doi: 10.1002/14651858. CD002831.pub2

Xu, Z., Huang, F., Kosters, M., and Rusch, N. (2017). Challenging mental health related stigma in China: Systematic review and meta-analysis. II. Interventions among people with mental illness. *Psychiatry Res* 255**,** 457-464. doi: 10.1016/j.psychres.2017.05.002

Yehia, F., and El Jardali, F. (2015). Applying knowledge translation tools to inform policy: the case of mental health in Lebanon. *Health Res Policy Syst* 13**,** 29. doi: 10.1186/s12961-015-0018-7

Zhao, S., Sampson, S., Xia, J., and Jayaram, M.B. (2015). Psychoeducation (brief) for people with serious mental illness. *Cochrane Database Syst Rev***,** Cd010823. doi: 10.1002/14651858.CD010823.pub2

Supplementary Materials

Data Sheet 1 - Search strategy

1. Community Mental Health Services.mp. or exp Community Mental Health Services/
2. Case Management.mp. or exp Case Management/
3. Managed Care Programs.mp. or exp Managed Care Programs/
4. Community Mental Health Centers.mp. or exp Organizational Case Studies/ or Patient Care Team/ 5. Community Mental Health Centers.mp. or exp Community Mental Health Centers/
6. Psychoeducation
7. Community mental health team
8. Crisis intervention
9. Housing support
10. Mental Disorders.mp. or exp Mental Disorders/
11. deinstitutionalization.mp. or exp Deinstitutionalization/
12. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9
13. 10 and 12
14. 11 and 13
15. limit 14 to “review articles”

SUPPLEMENTARY MATERIAL

Table S1 – Included studies

Table S.1: Included studies (for strategy 1 – Psychoeducation).

Author, Year	Type and number of primary studies	Number of participants	Countries (studies)	Intervention	Comparator	Type of outcomes measure	Primary outcomes	AMSTAR 2
STRATEGY 1 – PSYCHOEDUCATION								
Pilling, 2002	randomized controlled trials (18)	1,467	not reported	family interventions: i. psychoeducational intervention; problem solving crisis management work; or, intervention with the identified patient; ii. cognitive behavior therapy.	standard care or active care	at least 6 weeks	**Family interventions versus standard care:** **-relapse in first 12 months** (OR: 0.37, 95% CI: 0.23 to 0.60; NNT=6); **-relapse in follow-up 4-15 months after the end of the treatment, single family treatment** (OR: 0.70, 95% CI: 0.7 to 1.76); -**readmissions in first 12 months** (OR: 0.43, 95% CI: 0.08 to 2.28); **-readmissions in the first 2 years, single family interventions** (RR: 0.39, 95% CI: 0.11 to 1.34, NNT=9); **-readmissions in follow-up up to 2 years after** (OR: 1.08, 95% CI: 0.64 to 1.83, NNT= -18); -**suicide** (OR:0.88, 95% CI: 0.33 to 2.32);	Critically low

							-**burden** (WMD: -0.14, 95% CI: -0.76 to 0.47); -**burden, single family treatment** (WMD: -0.42, 95% CI: -0.88 to 0.03); -**expressed emotion** (RR: 0.90, 95% CI: 0.48 to 1.72, p= 0.38); -**compliance with medication** (RR: 0.63, 95% CI: 0.40 to 1.01, p= 0.65); **Family interventions versus all other treatments:** **-relapse in first 12 months** (OR: 0.52, 95% CI: 0.31 to 0.89) **-relapse in first 2 years, single family treatment** (OR: 0.57, 95% CI: 0.18 to 1.82) **-readmissions in first 12 months** (OR: 0.38, 95% CI: 0.10 to 1.40) **-readmissions in first 12 months, single family intervention** (OR: 0.22, 95% CI: 0.09 to 0.51) -**readmissions in first 2 years** (OR: 0.47, 95% CI: 0.23 to 0.96) **-compliance with medication** (OR: 0.63, 95% CI: 0.40 to 1.01) **Family interventions versus active treatments:**	

							-relapse in first 12 months (OR: 1.67, 95% CI: 0.71 to 0.31)	
Lincoln, 2007	randomized controlled trials (18)	1,534	Great Britain (5); China (4), Germany and Switzerland (3), Greece (1), Scandinavia (2), USA and Canada (3).	Psychoeducation with a focus on conveying relevant information about the disorder and its treatment while promoting better coping.	non-active group (waiting-list, treatment usual, or a non-specific intervention without proven effectiveness, e.g., problem solving; supportive treatment, leisure time groups)	follow-up 6 months; 7–12 months, >12 months	**Post-assessment:** -**relapse/ rehospitalization** (d= 0.53, 95% CI: 0.12- 0.95, p= 0.01); -**symptoms** (d=0.29, 95% CI: −0.13–0.70, p= 0.08); -**functional outcome** (d= −0.03, 95% CI: −0.84–0.78, p= 0.97); -**knowledge** (d= 0.48, 95% CI: 0.12–0.83, p= 0.00); -**medication adherence** (d=−0.25, 95% C: −1.25–0.75, p= 0.31); **Follow-up ≤ 6 months:** -**relapse/ rehospitalization** (d= 0.35, 95% CI: 0.14–0.55, p= 0.00); **Follow-up 7–12 months:** **-relapse/ rehospitalization** (d= 0.48, 95% CI: 0.15–0.82, p=0.00); - **symptoms** (d=0.19, 95% CI: −0.16–0.55, p= 0.14); - **functional outcome** (d= −0.19, 95% CI: −0.59–0.97, p= 0.32); **Follow-up > 12 months:**	Low

							-relapse/ rehospitalization (d=0.21, 95% CI: −0.07–0.49, p= 0.07) **Psychoeducation with family:** **-symptoms at post-assessment** (d=0.33, 95% CI: −0.26–0.93, p= 0.14) **-relapse/rehospitalizations at 7–12 month-follow-up** (d= 0.48, 95% CI: 0.10–0.85, p= 0 .00) **Psychoeducation without family:** **-symptoms at post-assessment** (d= 0.24, 95% CI: −0.39–0.86, p= 0 .23) -**relapse/rehospitalizations at 7–12 month-follow-up** (d=0.18, 95% CI: −0.47–0.82)	
Xia, 2011	randomized controlled trials (44)	5,142	China (32) France (1) USA (3) Canada (1), Germany (2) UK (3) Demark (1) Malaysia (1)	psychoeducation (didactic interventions or patient teaching involving individuals or groups)	standard care (normal level of psychiatric care provided in the area where the trial was carried out).	short term: up to 12 weeks), medium term: 13-52 weeks, long term: over 52 weeks	**- compliance with medication in short term** (RR: 0.52, 95% CI: 0.40 to 0.67; I^2=1%); **medium term** (0.36; 95% CI: 0.27 to 0.49; I^2= 0%); **long term** (RR: 0.48, 95% CI: 0.31 to 0.75; I^2= 78%); -**compliance with follow up in medium term** (RR: 1.00, 95% CI: 0.79 to 1.26; I^2= 30%), **long term by 2 years** (RR: 0.87, 95% CI: 0.62 to 1.10; I^2= 0%), **long term by 5 years or more** (RR: 0.77, 95% CI: 0.48 to 1.23; I^2= 0%)	Moderate

							-relapse for any reason in medium term (RR: 0.70, 95% CI: 0.61 to 0.81; I^2= 59%); **long term** (RR: 0.73, 95% CI: 0.62 to 0.85; I^2= 31%); -**satisfaction with the service** (RR: 0.24, 95% CI: 0.12 to 0.50);	
Zhao, 2015	randomized controlled trials (20)	2,337	China (10) Germany (3) UK (2) Italy (1) Malaysia (1) Pakistan (1) Denmark (1) Jamaica (1)	brief psychoeducation (didactic interventions or patient teaching) with 10 or less sessions;	standard care (normal level of psychiatric care provided in the area where the trial was carried out)	short term: up to 12 weeks, medium term: 13-52 weeks, long term: over 52 weeks	**- compliance with medication in short term** (RR: 0.63, CI: 0.41 to 0.96); **medium term** (RR: 0.17, 95% CI: 0.05 to 0.54); - **compliance with follow-up in short term** (RR: 1.00, CI: 0.24 to 4.18), **medium term** (RR: 0.74, 95% CI: 0.50 to 1.09), **long term** (RR: 1.19, 95% CI: 0.83 to 1.72) **- relapse in medium term (**RR: 0.70, 95% CI: 0.52 to 0.93)	High

Table S.1 (continued): Included reviews (for strategy 2 – Anti-stigma programs).

Author, Year	Type and number of primary studies	Number of participants	Countries (studies)	Intervention	Comparator	Type of outcome measure	Primary outcomes	AMSTAR 2
STRATEGY 2 –ANTI-STIGMA PROGRAMS								
Tsang, 2016	randomized controlled trials (7); controlled clinical trials (3); uncontrolled studies without a control group (4);	1,131	US (5) Canada (2) Israel (1); Japan (1); Turkey (1); Hong Kong (1); Switzerland (1); Netherlands (1); Austria (1)	psychoeducation combined with cognitive behavioral therapy, group discussion element (photovoice and coming out proud), social skills training element, narrative enhancement or cognitive therapy elements	no active treatment; usual treatment	10-40 sessions	**Psychoeducation versus usual treatment:** **- changes in internalized stigma of mental illness** (SMD= -0.40, 95% CI: -0.64 to -0.16, I^2= 17%, p= 0.001) **Self-stigma reduction program (photovoice, narrative enhancement/ cognitive therapy, recovery oriented) versus usual treatment:** - **reduction in total internalized stigma of mental illness total score** (SMD= -0.43, 95% CI: -0.72 to -0.14, I^2= 22%, p= 0.003)	Critically Low
Wood, 2016	randomized controlled trials (7), controlled trials (2) and cohort studies (3)	714	USA (4); UK (2); Canada (1); Hong Kong (1); Switzerland (1); Portugal (1); Japan (1); Israel (1)	Psychosocial interventions (including cognitive behavior therapy, psychoeducation and social skills training)	Standard care or usual care, waiting list control or Newspaper Reading group	The average number of sessions offered by the RCTs was 12.71 sessions (range 3–20), and 11.4 (range 6–20) by other studies. The majority of studies utilized a group format	**- improvement in internalized stigma at the end of the therapy** was not significant = (Hedges' g 0.24, 95% CI: -0.06 to 0.53, p=0.11) **-improvement in internalized stigma at follow up (3 weeks to 4 months)** was not significant (Hedges' g 0.21, 95% CI: −0.08 to 0.50, p = 0.16)	Low

						intervention and only one study offered individual therapy		
Xu, 2017	randomized controlled trials (15), controlled trials (2)	2,373	China (16); Hong Kong (1)	Psychoeducation + usual psychiatric care or Cognitive Behavioral Therapy + usual psychiatric care	usual psychiatric care	4 weeks – 1 year or from 5 – 24 sessions	**Psychoeducation or Cognitive Behavioral Therapy versus usual psychiatric care:** **-effects on perceived/experienced/ anticipated stigma** (SMD: 0.84, 95% CI: 0.54 to 1.14, I^2= 87%, p< 0.001) **-effects on self-prejudice** (SMD: 0.72, 95% CI: 0.51 to 0.93; I^2= 51%, p< 0.01) **- effects on stigma coping** (SMD: 0.86, 95% CI: 0.60 to 1.15, I^2= 74%, p< 0.01) -**improve on quality of life** (SMD: 0.75, 95% CI: 0.23 to 1.26; I^2= 84%, p=0.004) -**improve on depression symptoms** (SMD: 0.77, 95% CI: 0.25 to 1.30, I^2= 89%, p< 0.01) - **improve on anxiety symptoms** (SMD: 0.57, 95% CI: 0.34 to 0.81; I^2= 29%, p< 0.01) **Subgroup analysis:** Cognitive Behavioral Therapy (k=6, SMD: 0.90, 95% CI: 0.31 to 1.49) had a similar effect as psychoeducation (k=8, SMD: 0.80, 95% CI: 0.46 to 1.41) on perceived/ experienced/	Critically low

							anticipated stigma (χ2 =0.08, p=0.77). Psychoeducation (k=3, SMD: 0.82, 95% CI: 0.67 to 0.96) was more effective than Cognitive Behavioral Therapy (k=1, SMD: 0.29, 95% CI: −0.20 to 0.78) in reducing self-prejudice (χ2 =4.09, p=0.04). Cognitive Behavioral Therapy (k=1, SMD: 2.47, 95% CI: 1.80 to 3.14) was superior to psychoeducation (k=7, SMD: 0.72, 95% CI: 0.60 to 0.83) in improving coping with stigma (χ2=25.79, p< 0.01).	
Morgan, 2018	randomized controlled trials (62)	9,002	North America (32); Europe (22); Asia (4); Australia (3); South America (1)	contact interventions, educational interventions, mixed contact and education, family psychoeducation programs, and hallucination simulations	waitlist, no intervention, treatment as usual or attention control	Duration of contact varied 1 - 105 min, with a median of 15 min. The any anti-stigmatising effects were not examined beyond eight weeks, with most follow-ups only one week after the intervention	**Post Intervention:** **Contact interventions**: -**reductions in stigmatising attitudes:** (d=0.39, 95% CI: 0.22 to 0.55) and **desire for social distance** (d=0.59, 95% CI: 0.37 to 0.80) **Education interventions:** **-reductions in stigmatising attitudes** (d=0.30, 95% CI: 0.14 to 0.47) **and desire for social distance** (d=0.27, 95% CI: 0.08 to 0.46) **Mixed contact & education interventions:** **-reductions in stigmatising attitudes** (d= 0.32, 95% CI: 0.08 to 0.56) **and desire for social**	Low

							distance (d=0.43, 95% CI: 0.01 to 0.86) - **Family psychoeducation**: - **reductions in stigma post-intervention** (d=0.41, 95% CI: 0.11 to 0.70). **Follow up ≤ 6 months:** -effects were not significant in any type of intervention.	

Table S.1 (continued): Included reviews (for strategy 3 – Intensive case management).

Author, Year	Type and number of primary studies	Number of participants	Countries (studies)	Intervention	Comparator	Type of outcomes measure	Primary outcomes	AMSTAR 2
	STRATEGY 3: INTENSIVE CASE MANAGEMENT							
Burns, 2007	randomized controlled trials (29)	1,996	not reported	intensive case management (caseload up to and including 20)	standard care (from a community mental health team or outpatient clinic) or low intensity case management (caseload greater than 20) in people with severe mental disorder living in the community	not reported	-**hospital use at baseline** (coefficient −0.23, 95% CI: −0.36 to −0.09, p=0.001); -**hospital use in control groups** (coefficient −0.44, 95% CI: −0.57 to −0.31);	Low
Dieterich, 2017	randomized controlled trials (40)	7,524	Australia, Canada and USA (27); Europe (12); China (1);	Intensive case management (package of care shaped on the Assertive Community Treatment model, Assertive Outreach model or Case Management model; with a caseload up to 20 people)	**non-intensive case** (package of care shaped on the Assertive Community Treatment model, Assertive Outreach model or Case Management model; with over 20 people) or standard care community or outpatient model of care not specifically shaped on either the model of	short term (up to 6 months), medium term (7- 12months), and long term (over 12 months).	**Intensive case management versus standard care:** **-reduced mean of the number of days in hospital per month** (MD: -0.86, 95% CI: -1.37 to -0.34); **-outcome global state** (RR: 0.68, 95% CI: 0.58 to 0.79) **-reducing death by suicide** (RR: 0.68, 95% CI: 0.31 to 1.51) -**social functioning the effect on unemployment** (RR: 0.70, 95% CI: 0.49 to 1.0); -**participant satisfaction** by short term (RR:6.20, 95% CI:	High

					Assertive Community Treatment and Case Management, and not working within a designated named package or approach to care)		2.60 to 9.80); by medium term (RR: 1.93, 95% IC: 0.86 to 3.01, I^2=0%); and by long term (RR: 3.23, 95% CI: 2.31 to 4.14; I^2=0%); **Intensive case management versus no standard care:** **-reduced mean of the number of days in hospital per month** (MD: -0.08, 95% CI: -0.37 to 0.21); -**reducing death by suicide** (RR: 0.88, 95% CI: 0.27 to 2.84); **-social functioning the effect on unemployment** (RR: 1.46, 95% CI: 0.45 to 4.74)	

Table S.1 (continued): Included reviews (for strategy 4 – Community mental health teams).

Author, Year	Type and number of primary studies	Number of participants	Countries (studies)	Intervention	Comparator	Type of outcomes measure	Primary outcomes	AMSTAR 2
	STRATEGY 4 - COMMUNITY MENTAL HEALTH TEAMS							
Malone, 2007	randomized controlled trials (3)	587	UK (3)	management of care from community mental health team	Standard or usual care (normal care in the area concerned, non-team community care)	3- 12 months	-**death** by suicide and in suspicious circumstances (RR: 0.49, 95% CI: 0.1 to 2.2; I^2= 0%) **-leaving study early or up to 12 months** (RR: 1.10, 95% CI: 0.68 to 1.78, I^2= 0%) -**hospital admission** (RR: 0.81, 95% CI: 0.67 to 0.97, I^2= 28%) -**satisfaction with the service** (RR:0.37, 95% CI: 0.18 to 0.79) -**service use -use of Accident and emergency and general hospital up to 12 months:** (RR: 0.86, 95% CI: 0.66 to 1.12, I^2= 44%) -**service use – contact with primary care up to 12 months** (RR: 0.94, 95% CI: 0.80 to 1.11, I^2= 0%) -**service use – contact with social services up to 12 months** (RR: 0.76, 95%: CI 0.58 to 1.01, I^2= 0%) -**social functioning– police contacts** (RR: 2.07, 95% CI: 1.08 to 3.97, I^2=53%)	Moderate

Table S.1 (continued): Included reviews (for strategy 5 – Assisted living).

Author, Year	Type and number of primary studies	Number of participants	Countries (studies)	Intervention	Comparator	Type of outcome Measure	Primary outcomes	AMSTAR 2
	STRATEGY 5 – ASSISTED LIVING							
Leff, 2009	randomized controlled trials (6); other design not reported (38)	13,436	not reported	model housing (residential care and treatment housing; supported housing interventions; permanent Supported housing)	Non-model housing	6 months to 5 years	**Residence care and treatment versus non-model housing:** **-housing stability:** (effect size= 0.48, p< 0.05) **-reduction in psychiatric symptoms:** (effect size= 0.65, p<0.05) **-reduction in hospitalization:** (effect size= 0.34, p< 0.05) **-reduction in alcohol abuse:** (effect size= 0.87, p> 0.05) **-reduction in drug abuse:** (effect size= 0.41, p> 0.05) **-increased employment:** (effect size= 0.27, p> 0.05) **-increased satisfaction:** (effect size= 0.07, p> 0.05) **Residential continuum versus non-model housing:** -**housing stability:** (effect size= 0.80, p< 0.05)	Low

							-**reduction in psychiatric symptoms:** (effect size= 0.68, p> 0.05) -**reduction in alcohol abuse:** (effect size=0.07, p> 0.05) -**reduction in drug abuse:** (effect size=0.3, p> 0.05) -**increased satisfaction:** (effect size=0.55, p> 0.05) **Permanent Supported Housing versus non-model housing:** **-housing stability:** (effect size=0.63, p< 0.05) **-reduction in psychiatric symptoms:** (effect size= 0.08, p> 0.05) **-reduction in hospitalization:** (effect size= 0.72, p< 0.05) -**reduction in alcohol abuse:** (effect size= 0.21, p> 0.05) -**reduction in drug abuse:** (effect size= 0.51, p> 0.05) **-increased employment:** (effect size= 0.27, p> 0.05) -**increased satisfaction:** (0.73, p< 0.001) **Non-model housing:**	

							-**housing stability:** (effect size= -0.63, p> 0.05) -**reduction in psychiatric symptoms:** (effect size= -0.11, p> 0.05) **-reduction in hospitalization:** (effect size= -0.33, p> 0.05) **-reduction in alcohol abuse:** (effect size= 0.06, p> 0.05) -**reduction in drug abuse:** (effect size= 0.2, p> 0.05) **-increased satisfaction:** (effect size= -0.38, p> 0.05)	
McPherson, 2018	Total in "deinstitutionalization" subgroup = 28: cohort studies (24), quasi-experimental (2), single case control (1), randomized controlled trial (1) Total in review= 115	6,516 (but one of study did not declare the total number of participants)	not reported separately	mental health supported accommodation (defined as any service that provided support, delivered predominately by non-professionally qualified staff, to people with mental health problems living in community-based accommodation, either alone or in shared settings)	none or accommodation settings (at home with family or friend, in own house), other type of model accommodation	6 months to 13 years of follow up	Due to the heterogeneity of the retrieved studies, in terms of the design of the study, type of supported housing, population, and outcomes, the data were unfeasible to summarized. Synthesis narrative of high and moderate quality studies suggested a trend toward improvement in symptoms, social functioning, stability and in a reduction the rate of hospitalization	Low

Table A.1 (continued): Included reviews (for strategy 6 – Interventions for acute psychiatric episodes).

Author, year	Type and number of primary studies	Number of participants	Countries (studies)	Intervention	Comparator	Type of outcome measure	Primary outcomes	AMSTAR 2
	STRATEGY 6 - INTERVENTIONS FOR ACUTE PSYCHIATRIC EPISODES							
Murphy, 2015	randomized controlled trials (8)	1,144	Australia (1); Canada (2); USA (2); UK (3)	crisis intervention (any type of crisis-orientated treatment of an acute psychiatric episode by staff with a specific remit to deal with such situations, in and beyond 'office hours')	standard care (normal care given to those suffering from acute psychiatric episodes in the area concerned)	3 months – 2 years	-**reduction of repeat admissions to hospital at six months** (RR: 0.75, 95% CI: 0.50 to 1.13; I^2= 80%); -**improve mental state according to Brief Psychiatric Rating Scale, three months** (MD: -4.03, 95% CI: -0.18 to 0.12); -**improve global state according to Global Assessment Scale, 20 months** (MD: 5.70, 95% CI: -0.26 to 11.66) -**satisfaction with the care, 20 months crisis according to Client Satisfaction Questionnaire** (MD: 5.40, 95% CI: 3.91 to 6.89) -**reduction of family burden at six months** (RR: 0.34, 95% CI: 0.20 to 0.59) -**quality of life scores at six months according to Manchester Short Assessment of quality of life** (MD: -1.50, 95% CI: -5.15 to 2.15)	High

Wheeler, 2015	Total studies (69), which 21 were used in quantitative analysis	14,833 (but, seven studies did not report total n)	Australia (3), Germany (1), USA (2), UK (15)	crisis resolution teams	usual treatment; another crisis resolution teams model	not reported	The quantitative synthesis was not feasible due to different designs of the retrieved studies such as type of studies, type of outcomes and settings. However, narrative synthesis suggests that crisis resolution teams reduce hospital admissions and recommend as key characteristics: 24 hours service provision, presence of a psychiatrist in the team, communication and integration with other local mental health services, high quality of training.	Low

SUPPLEMENTARY MATERIAL

Table S2 - Excluded studies

Table S2: Excluded studies.

Author, date	Reason for exclusion
Akiyama, 2008	Not a systematic review
Arboleda-Fiórez, 1998	Not a systematic review
Ashton, 2018	Not a systematic review
Appathurai, 1986	Not a systematic review
Aubry, 2015	Not a systematic review
Ayano, 2018	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Baptista, 2011	Focus only on patients with bipolar disorders
Bemak, 1985	Not a systematic review
Campbell, 2009	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Catty, 2002	Included in another more recent systematic review
Chan, 2009	Not a systematic review
Chilvers, 2010	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Collard, 2014	Not a systematic review
Dixon, 1995	Not a systematic review
Hazel, 2017	Not a systematic review
Hailemariam, 2016	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Henderson, 1998	Not a systematic review
Kanapp, 2011	Not comparison among strategies for outpatient follow-up and care
Kohrt, 2018	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Kozma, 2009	Focus only on adults with intellectual disorders
Kronenberg, 2017	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Kunitoh, 2013	Not a systematic review
Kyle,2008	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Ly, 2015	Not a systematic review
Lyman, 2014	Not a systematic review
Marshall,2011	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Mascayano, 2016	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Mccrone, 2009	Not a systematic review
Mittal, 2012	Not a systematic review
O'Campo, 2009	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Peterson, 2013	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Petrello, 2017	Not a systematic review

Petretto, 2013	Not a systematic review
Ramonet, 2013	Not a systematic review
Ran, 2003	Not a systematic review
Reily, 2013	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Roy,2014	Not a systematic review
Ryu, 2006	Not a systematic review
Sampaio, 2006	Not a systematic review
Shah, 2014	Focus only on patients with stress
Simmonds, 2001	Included in another more recent systematic review
Tursi, 2013	Focus only on patients with depression
Vazquez-Bourgon, 2012	Not a systematic review
Wash, 2010	Focus only on adults with intellectual disorders
White, 2018	Not an outpatient care strategy or follow-up for deinstitutionalized patients (systematic review protocol)
Winters, 2015	Not a systematic review
Winkler, 2016	Not an outpatient care strategy or follow-up for deinstitutionalized patients
Worral, 2018	Not a systematic review
WHO, 2014	Not a systematic review
Ziguras, 2000	Not an outpatient care strategy or follow-up for deinstitutionalized patients

SUPPLEMENTARY MATERIAL –

Table S3 – AMSTAR results.

Table S3: Critical appraisal of studies included using the AMSTAR 2 tool.

Author, year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Q15	Q16	Ranking of quality[&]
STRATEGY 1: PSICOEDUCACION																	
Pilling 2002	Y	NA**	N	N	Y	Y	N	Y	N	N	Y	N	N	Y	NA*	N	Critically low
Lincoln 2007	Y	NA**	N	PY	Y	Y	N	Y	PY	N	Y	Y	Y	Y	Y	Y	Low
Xia2011	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Moderate
Zhao 2015	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA*	Y	High
STRATEGY 2: ANTI-STIGMA PROGRAMS																	
Wood 2016	Y	Y	N	PY	N	N	Y	Y	Y	N	Y	N	N	Y	NA*	Y	Low
Xu 2017	Y	Y	N	PY	Y	Y	N	PY	Y	N	Y	N	N	Y	Y	N	Critically low
Tsang 2016	Y	N	N	PY	Y	Y	N	Y	Y	N	Y	Y	Y	N	NA*	N	Critically low
Morgan 2018	Y	Y	Y	PY	N	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
STRATEGY 3: INTENSIVE CASE MANAGEMENT																	
Burns 2007	Y	NA**	N	PY	Y	Y	N	N	Y	N	Y	Y	Y	Y	Y	Y	Low
Dieterich 2017	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	High
STRATEGY 4: COMMUNITY MENTAL HEALTH TEAMS																	
Malone 2017	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	NA*	Y	Moderate
STRATEGY 5: ASSISTED LIVING																	
Leff 2009	Y	NA**	N	Y	Y	Y	PY	PY	Y	N	Y	Y	Y	N	N	Y	Low
McPherson 2018	Y	Y	N	PY	Y	Y	N	Y	Y	N	NA	NA	Y	Y	NA	Y	Low
STRATEGY 6: INTERVENTIONS FOR ACUTE PSYCHIATRIC EPISODES																	
Murphy 2015	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA*	Y	High
Wheeler2015	Y	Y	Y	Y	Y	Y	N	PY	Y	N	NA	NA	Y	Y	NA	Y	Low

Y, yes; PY, partial yes; N, no; NA, not applicable; * funnel plot not applicable, because there were 10 or fewer studies per outcome; ** SR was published before PROSPERO registration started; PROSPERO was available virtually only in February 2011;

[&]High: no or one non-critical weakness; Moderate: more than one non-critical weakness; Low: one critical flaw with or without non-critical weaknesses; Critically low: more than one critical flaw with or without non-critical weaknesses

DOMAINS IN AMSTAR 2:

Q1: Did the research questions and inclusion criteria for the review include the components of PICO?
Q2 (critical domain): Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
Q3: Did the review authors explain their selection of the study designs for inclusion in the review?
Q4 (critical domain): Did the review authors use a comprehensive literature search strategy?
Q5: Did the review authors perform study selection in duplicate?
Q6: Did the review authors perform data extraction in duplicate?
Q7 (critical domain): Did the review authors provide a list of excluded studies and justify the exclusions?
Q8: Did the review authors describe the included studies in adequate detail?
Q9 (critical domain): Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?
Q10: Did the review authors report on the sources of funding for the studies included in the review?
Q11 (critical domain): If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
Q12: If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?
Q13 (critical domain): Did the review authors account for RoB in individual studies when interpreting/discussing the results of the review?
Q14: Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
Q15 (critical domain): If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
Q16: Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

SUPPLEMENTARY MATERIAL

Table S4 - Common barriers in mental health and possible solutions.

Table S.4: Common barriers in mental health and possible solutions.

Barriers	Possible solutions to barriers
Health care professionals	
-Professional resistance: rigid attitudes of professionals and reluctance to make any changes in their work (Shen et al., 2017). -Scarcity of qualified and credentialed mental health workers (Kakuma et al., 2011; Shen et al., 2017). - Deficiency of trained mental health team and poorly equipped staffed health care (Kakuma et al., 2011). -Ineffectiveness of multidisciplinary teams due to inconsistent practices or practices that are not documented clearly, poor communication, and lack of leadership (Woody et al., 2018).	-Strengthening institutional capacity to implement effective training programmes and continuous education (Kakuma et al., 2011). -Development of a new and wide range of cadres, delegating and shifting tasks within and across sectors (Kakuma et al., 2011). -Good communication within teams, defined leadership, and clear documentation practices (Woody et al., 2018).
Government officials	
-Lack of political priority and budgetary support for mental health (Shen et al., 2017). -Poor leadership and underqualified managers (Shen et al., 2017). -Enactment of mental health policies without real changes in practice (WHO, 2014).	-Need for political leaders with will, commitment and ownership (Shen et al., 2017). -Cooperation from all levels of government to develop, implement and review mental health policy and legislation (Bhugra et al., 2018).
Patients	
-Social stigma, discrimination, cultural beliefs, religious roots and negative societal responses (Stuart, 2016). -Self-stigma and isolation, (Tsang et al., 2016; Morgan et al., 2018). -Lack of public education (WHO, 2001). -Difficulties in entering the formal labour market (Kinoshita et al., 2013) and becoming involved in other activities.	-Public awareness and education campaigns focusing on the frequency of mental disorders, their treatment, recovery and the human rights of people with mental disorders (WHO, 2001). -Supported employment (Kinoshita et al., 2013). -Provision of different modes of occupation to give a sense of purpose to life (Burgoyne, 2014). -Peer support services (Walker and Bryant, 2013; Chinman M., 2014).
Others (Lack of partnership with other sectors and knowledge translation)	
-Lack of partnership formation with other sectors (Shen et al., 2017). -Knowledge–action gap: failure to incorporate science into routine healthcare practice and health policy (Shidhaye, 2015; Chinman et al., 2017). -Gap in indicators for mental health and the available information system, particularly in low- and middle-income countries. No or little data are available about mental health service needs, coverage, quality and resource demands (Upadhaya et al., 2016; Ahuja et al., 2018).	-Configuration of proactive partnerships with clearly defined roles and that pursue evidence-based innovations (WHO, 2001): i) partnerships between governments and non-governmental organizations and private practitioners (Shen et al., 2017); ii) partnerships among universities, agencies, and local and international organizations (WHO, 2001; Kakuma et al., 2011). -Adoption of scientific implementation frameworks to advance equity and decrease disparities (Chinman et al., 2017); this could be facilitated by an external team (Shidhaye, 2015). -Development and inclusion of standard indicators for mental health and a reporting system to monitor the coverage and quality of services (Ahuja et al., 2018).

5.2 Produtos da Parte II

5.2.1 Artigo científico 3 - *Switching between second-generation antipsychotics in patients with schizophrenia and schizoaffective disorder: 10-year cohort study in Brazil*

O artigo científico "*Switching between second-generation antipsychotics in patients with schizophrenia and schizoaffective disorder: 10-year cohort study in Brazil"* teve como objetivo identificar os fatores associados à troca de antipsicóticos de segunda geração em pacientes com esquizofrenia ou transtorno esquizoafetivo ao longo de dez anos.

A formatação seguiu as normas da revista *Frontiers in Pharmacology* e foi submetido em 04 de dezembro de 2020. Encontra-se em fase de revisão.

Revista: *Frontiers in Pharmacology*
ISSN: 1663-9812
Versão online: 1663-981
Fator de impacto: 4,2
Classificação Webqualis/Capes, área de Farmácia, 2020: A1

Comprovante de submissão do artigo encontra-se no **Anexo E.**

Switching between second-generation antipsychotics in patients with schizophrenia and schizoaffective disorder: 10-year cohort study in Brazil

Short title: Switching of second-generation antipsychotics

Izabela Fulone
Pharmaceutical Sciences Postgraduate Course, University of Sorocaba, UNISO, Sorocaba, São Paulo State, Brazil[1]
E-mail: bela.fulone@gmail.com

Marcus Tolentino Silva
Pharmaceutical Sciences Postgraduate Course, University of Sorocaba, UNISO, Sorocaba, São Paulo State, Brazil[1]
E-mail: marcus@gmail.com

Luciane Cruz Lopes (corresponding author)
Pharmaceutical Sciences Postgraduate Course, University of Sorocaba, UNISO, Sorocaba, São Paulo State, Brazil[1]
E-mail: luslopesbr@gmail.com; luciane.lopes@prof.uniso.br;

[1] University of Sorocaba
Rodovia Raposo Tavares, KM 92,5 - Sorocaba, São Paulo State, Brazil
ZIP Code: 18023-000
Phone: 55 19 99781-8441 Fax: 55 15 2101-7074

Declaration of Interest: none

Financial support: Fapesp, grants 2017/20668-7

Word count: 3009

Number of references: 44

Number of figures: 2

Number of tables: 2

ABSTRACT

Objective: Switching between second-generation antipsychotics (SGAs) is a common clinical practice in the treatment of schizophrenia and schizoaffective disorders due to differences in the drugs' tolerability and safety profiles as well as the challenge of obtaining an ideal response. However, the factors associated with SGA switching remain uncertain and related real-world data are scarce. The main objective was to identify the factors associated with the switching of SGAs in patients with schizophrenia or schizoaffective disorder.

Methods: We conducted a retrospective cohort study of outpatients with schizophrenia or schizoaffective disorder, who were aged ≥ 18 years and received a SGA (clozapine, olanzapine, risperidone, quetiapine or ziprasidone) from a Brazilian pharmaceutical assistance program for at least 3 months. We identified SGA users from 2008 to 2017 by using a national administrative database (Ambulatory Information System-SIA/SUS). The factors associated with the switches were evaluated by Cox proportional hazards regression and adjusted for sex and age; the confidence interval was set at 95% (95% CI).

Results: In total, 563,765 patients were included. Female sex, advanced age of ≥ 70 years, residence in the Brazilian northeast region, and the type of antipsychotic used were associated with an increased risk of switching ($p<0.001$). The incidence of switching ranged from 37.6/100 person-years for clozapine users to 58.2 /100 person-years for risperidone users. Compared to the adjusted hazard ratio, for clozapine users, the corresponding ratios for risperidone, ziprasidone, quetiapine and olanzapine were 1.59 (95% CI, 1.57 – 1.61), 1.41 (95% CI, 1.39 – 1.44), 1.25 (95% CI, 1.23 – 1.26) and 1.11 (95% CI, 1.10 – 1.12) respectively.

Conclusions: The groups most susceptible to SGA switching in real-life setting were older individuals, women, and those living in the Brazilian northeast region. The risk of switching associated with clozapine was lower than that associated with the other SGAs.

Keywords: Antipsychotics, agents; Schizophrenia; Schizoaffective disorder; Drug Substitution;

INTRODUCTION

Switching of antipsychotics in the treatment of schizophrenia or related psychotic disorders is a common clinical practice and has been recommended to ensure a more appropriate treatment option in the face of issues including efficacy, safety, or tolerability (Faries et al., 2009; Nyhuis et al., 2010). Therapeutic failure, including suboptimal improvement, persistence of negative or positive symptoms, worsening of certain symptoms or level of functioning, poor treatment adherence, and intolerable adverse reactions may determine the switch during treatment (Keks et al., 2019). The most common reasons for switching related to safety and tolerability, depending on the antipsychotic used, include weight gain, metabolic syndrome, sedation, hyperprolactinemia, anticholinergic effects, increased QT, and sexual dysfunction (Stroup and Gray, 2018)

The decision to switch from one antipsychotic to another should be made considering the possible risks associated with the switching process, such as relapses, exacerbation of some symptoms, new adverse effects, withdrawal syndromes, rebound, and serious drug interactions (Bernardo et al., 2011). Patients who switched antipsychotics were more likely to be hospitalized and use acute care services compared to patients continuing with the initial antipsychotic. In addition, switching resulted in poor clinical outcomes and higher total health care costs (Faries et al., 2009).

Antipsychotics switching could be influenced by various factors: in particular, factors related to the patient, illness, environment, antipsychotics availability, acceptability of treatment, and especially related to the medication (e.g., adverse events, drug interactions, therapeutic response) need to be evaluated (Buckley and Correll, 2008). First-generation and second-generation antipsychotics (SGAs) constitute heterogeneous groups of drugs with different receptor binding and affinity profiles, and hence, distinct clinical effects are expected (Cerovecki et al., 2013). Knowledge about the differences in the pharmacodynamic and pharmacokinetic characteristics of the previous and newer antipsychotics is crucial for adopting a more effective switching strategy, discontinuation strategy (abrupt discontinuation or tapering) for each agent, and optimization of the outcomes (Correll, 2010).

In case of an abrupt switch from an antipsychotic with high cholinergic affinity, such as olanzapine or clozapine, to that with a low affinity, cholinergic rebound

syndrome is likely (Cerovecki et al., 2013). Switching from antipsychotics with high affinity for histaminergic receptors to those with low affinity will result in rebound insomnia (Buckley and Correll, 2008). Similarly, switching from clozapine to any other antipsychotic, can lead to serious withdrawal effects and rebound psychosis (Ganguli, 2002; Keks et al., 2019).

Currently, the Brazilian National Health System (SUS) provides SGAs (clozapine, olanzapine, quetiapine, risperidone and ziprasidone) to patients with a diagnosis of schizophrenia or related psychotic disorders, refractory to treatment with first-generation antipsychotics, and who are enrolled in the pharmaceutical assistance program. SGAs are considered high-cost medicines and are dispensed and funded by the SUS after an analysis of compliance with the National Clinical Guidelines (Brazil, 2013; Brazil, 2014).

The costs of the treatment of schizophrenia are high worldwide, particularly pharmacological therapy (Santos, 2017). SGAs are responsible for the high cost of treatment for schizophrenia through SUS (Lindner et al., 2009). Patients refractory to other antipsychotics tend to undergo antipsychotics switching and have psychotic outbreaks followed by hospitalizations, which result in a significant economic burden in Brazil (Barbosa et al., 2018). A cohort study conducted in Brazil from 2000 to 2010 showed that olanzapine accounted for approximately 63% of the total costs of SGAs and that patients who used clozapine had the highest mean annual cost per patient for outpatient psychiatric care and hospitalization (Barbosa et al., 2018).

However, despite the burden and risks, few studies have explored the factors associated with switching antipsychotics in the treatment of schizophrenia and other psychotic disorders (Nyhuis et al., 2010; Xu and Krishnaswamy, 2018). Therefore, the goal of this study was to investigate the factors associated with switching of SGAs in patients with schizophrenia or schizoaffective disorder in Brazil.

METHODS

Study design

This was a retrospective cohort study conducted in all patients who were on SGAs for schizophrenia or schizoaffective disorder treatment and received these medicines through a pharmaceutical assistance program from the SUS, from January 2008 to December 2017.

Setting

The cohort was conducted using register-based data from a nationwide administrative database (Ambulatory Information System, SIA/SUS), where in information regarding all outpatient care procedures is collected, and processed and which is used for providing high-cost medicines or procedures for specific diseases according to Brazilian guidelines. The database represents over 200 million procedures/month (BRAZIL, 2008). These individualized secondary data are publicly available (unrestricted access) and were available from 2008.

SGAs are considered expensive medicines, and patients get access to these medicines via SUS only after requests for these medicines are analyzed and are in compliance with Brazilian guidelines for the treatment of schizophrenia and schizoaffective disorders. Via the SUS, SGA are provided to patients monthly for a period of 3 months. Therefore, the quantity prescribed could cover only a maximum duration of 3 months. For this reason, we adopted the 90-day cut-off. After this period, a new request and analysis are necessary according to the rule in Brazil. Currently, the following SGAs are available through the SUS: oral clozapine, olanzapine, quetiapine, risperidone, and ziprasidone. Aripiprazole or injectable SGAs are not available through the SUS.

Brazilian guidelines recommend SGA monotherapy and the use of clozapine only in cases in which patients are refractory to at least two other antipsychotics (Brazil, 2013).

The data for the study were gathered between January 2008 and December 2017.

Participants

The study included all patients aged ≥ 18 years, who were identified from SIA/SUS database, received SGAs (clozapine, olanzapine, quetiapine, risperidone, or ziprasidone) for more than 90 days, during January 2008 to December 2017, and diagnosed with one of the following diseases according to International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10): Paranoid schizophrenia (F20.0), Hebephrenic schizophrenia (F20.1), Catatonic schizophrenia (F20.2), Undifferentiated schizophrenia (F20.3), Post-schizophrenic depression (F20.4), Residual schizophrenia (F20.5), Simple schizophrenia (F20.6),

Other schizophrenia (F20.8), Schizoaffective disorder, manic type (F25.0), Schizoaffective disorder, depressive type (F25.1), Schizoaffective disorder, depressive type (F25.2).

Variables

The baseline demographic variables considered were sex, age at cohort entry, race, geographic region of residence at study entry, and year of cohort entry (defined as the year of the first provision of SGAs from January 1, 2008, to December 31, 2017). The baseline clinical variables considered were SGA used at cohort entry, diagnosis according to ICD-10 at cohort entry and mean treatment duration (months).

Outcomes

The primary outcome was defined as the switch between SGAs. The following were considered as possible factors associated with SGA switching: i) sex, ii) age, iii) year of cohort entry (2008-2017), iv) geographic region of residence; v) diagnosis according to ICD-10 codes, and vi) SGA used at study entry (clozapine, risperidone, quetiapine, ziprasidone and olanzapine).

Data source/measurement

The data on all the patients identified were gathered from the registers of the nationwide database SIA/SUS. The records were linked by the National Health Card number for follow-up using deterministic linkage.

The first date of SGA provision identified in the SIA/SUS database during the period from January 1, 2008, to December 31, 2017, was considered as the cohort entry date. Some patients might already have received SGAs when they entered the cohort.

During the 10-year study period, all patients were followed up until the last patient record in the SIA/SUS or death.

Statistical analysis

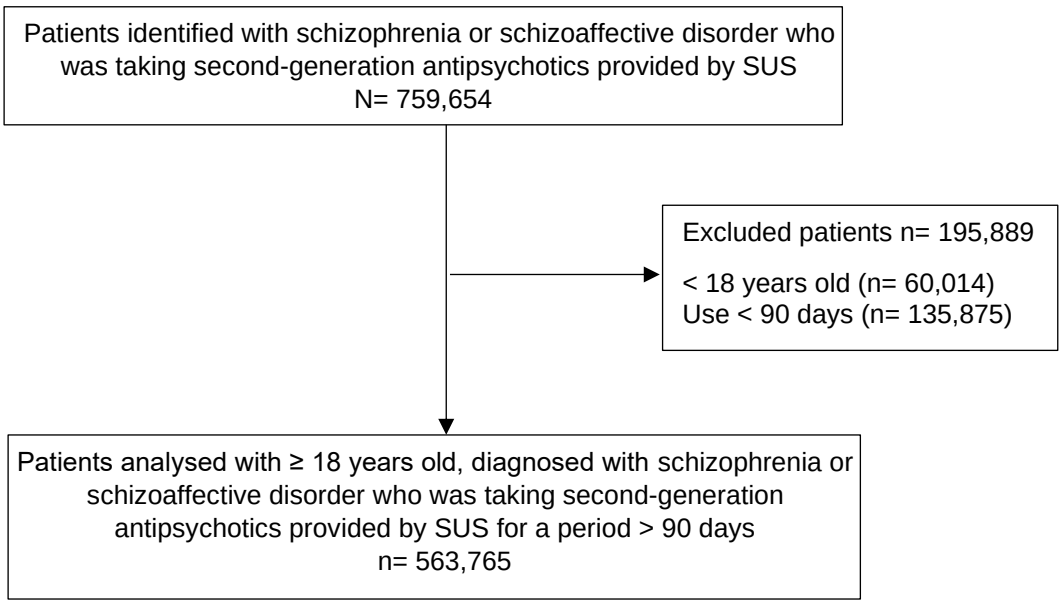
Continuous variables were expressed as mean ± standard deviation (SD), and categorical variables as percentages for descriptive statistics. Pearson’s Chi squared

test was performed to analyze correlations between switches and categorical variables. Incidence rates of switches were calculated as cumulative incidence (events/100 patient-years) and compared using the hazard ratio. Absence of switches was estimated using the Kaplan-Meier method. Log rank test was used to assess the significance of differences between absence of switches curves. Cox regression analysis was performed to analyze the association of age, sex, year of cohort entry, geographic region of residence, diagnosis and SGA used at cohort entry. A multivariable Cox proportional-hazards regression model adjusted by sex and age was used to examine the hazard ratios of the included factors. All tests were two-tailed. Confidence intervals of 95% and a significance level of $p < 0.05$ were used. All statistical analyses were performed using Stata 14.2.

RESULTS

We identified 759,654 patients with schizophrenia or schizoaffective disorder who were on SGA provided by the SUS from 2008 to 2017. From among these patients, 25.5% were excluded due to their age or time of use of SGA. A total of 563,765 patients met the inclusion criteria and were included in the cohort **Figure 1**.

Figure 1 - Flow chart of study.



Most of the patients were women (51.6%), the mean patient age at study entry was 46.4 (±18.6) years, lived in the south of Brazil (60.3%) and the most commonly diagnosed disorder was paranoid schizophrenia (78.2%). The most commonly used SGA at study entry was olanzapine (31.8%), followed by risperidone (29.2%), quetiapine (28.4%), ziprasidone (5.3%), and clozapine (5.2%). The mean follow-up duration was 39 (±33.6) months, **Table 1**.

There were sex, age, residence region, and treatment length related differences in the frequency of the SGA used. Clozapine, olanzapine, and risperidone were the most often prescribed SGA among men in the entry of the study. The proportion of quetiapine and ziprasidone use among women was higher than that in men.

Quetiapine was more frequently used by elderly individuals aged higher than 60 years, and the frequency of use increased progressively with advancing age (60-69 years: 34.2%; 70-79 years: 48.6%; ≥ 80 years: 62.7%).

The frequency of SGA use differed among the various regions of Brazil. In the southeast region, quetiapine (32.4%) and risperidone (29.8%) were the most used, while in the northeast region, the most commonly used SGAs were olanzapine and risperidone. The mean treatment duration varied from approximately 33 months for quetiapine to 49 months for clozapine.

Table 1: Demographic and clinic characteristics of study participants according second-generation antipsychotics used.

Variables	clozapine n= 29,466 (%)	olanzapine n= 179,486 (%)	risperidone n= 164,612 (%)	quetiapine n= 159,989 (%)	ziprasidone n= 30,212 (%)	Total 563,765
Sex						
Male	18,450 (6.7)	99,416 (36.4)	84,188 (30.8)	58,309 (21.3)	12,516 (4.6)	272,879
Female	11,016 (3.8)	80,070 (27.5)	80,424 (27.6)	101,680 (34.9)	17,696 (6.1)	290,886
Mean age (SD)						
	38.91 (±13.2)	42.65 (±16.1)	45.82 (±18.4)	54.42 (±20.6)	40.55 (±12.9)	46.61 (±18.6)
Age group at cohort entry (years)						
18-29	8,133 (7.1)	43,640 (37.9)	36,613 (31.8)	20,050 (17.4)	6,709 (5.8)	115,145
30-39	8,610 (7.2)	42,360 (35.7)	33,360 (28.1)	25,998 (21.9)	8,372 (7.0)	118,700
40-49	6,665 (5.9)	38,166 (33.9)	32,372 (28.8)	27,275 (24.3)	7,895 (7.0)	112,373
50-59	3,844 (4.5)	27,716 (32.7)	24,924 (29.5)	23,231 (27.5)	4,894 (5.8)	84,609
60-69	1,454 (3.0)	14,203 (29.2)	14,630 (30.1)	16,602 (34.2)	1,645 (3.4)	48,534
70-79	560 (1.3)	8,447 (19.5)	12,692 (29.3)	21,062 (48.6)	519 (1.2)	43,280
≥ 80	200 (0.5)	4,954 (12.0)	10,021 (24.4)	25,771 (62.7)	178 (0.4)	41,124
Race						
White	3,362 (5.3)	17,286 (27.2)	16,130 (25.4)	24,316 (38.2)	2,478 (3.9)	63,572
Black	208 (3.9)	1,898 (36.2)	1,547 (29.5)	1,345 (25.6)	248 (4.7)	5,246
Pardo	1,877 (5.6)	12,099 (36.1)	8,726 (26.0)	9,562 (28.5)	1,278 (3.8)	33,542
Yellow	628 (5.3)	4,617 (39.1)	2,782 (23.5)	3,370 (28.5)	413 (3.5)	11,810
Indigenous	3 (3.9)	16 (21.0)	30 (39.5)	33 (43.4)	5 (6.6)	76
No information	23,388 (5.2)	143,570 (31.9)	135,397 (30.1)	121,374 (27.0)	25,790 (5.7)	449,519
Year of cohort entry						
2008	9,167 (7.3)	49,423 (39.2)	40,030 (31.8)	16,746 (13.3)	10,622 (8.4)	125,988
2009	1,816 (3.6)	15,753 (31.8)	16,296 (32.9)	12,053 (24.3)	3,659 (7.4)	49,577
2010	2,049 (4.2)	13,148 (26.7)	16,328 (33.2)	14,294 (29.1)	3,331 (6.8)	49,150
2011	2,480 (4.9)	12,284 (24.6)	18,139 (36.4)	13,991 (28.1)	2,983 (5.9)	49,877
2012	1,700 (4.1)	10,610 (25.8)	13,722 (33.3)	13,214 (32.1)	1,915 (4.6)	41,161
2013	1,903 (4.2)	13,084 (29.0)	12,942 (28.7)	15,432 (34.2)	1,745 (3.9)	45,106
2014	1,730 (3.7)	14,125 (30.0)	12,684 (26.9)	17,170 (36.5)	1,280 (2.7)	46,989
2015	3,060 (5.1)	19,525 (32.8)	13,154 (22.1)	21,954 (36.8)	1,883 (3.2)	59,576

Table 1 (continuation): Demographic and clinic characteristics of study participants according second-generation antipsychotics used.

Variables	clozapine n= 29,466 (%)	olanzapine n= 179,486 (%)	risperidone n= 164,612 (%)	quetiapine n= 159,989 (%)	ziprasidone n= 30,212 (%)	Total 563,765
2016	3,944 (6.4)	20,298 (32.7)	13,699 (22.1)	21,936 (35.4)	2,142 (3.4)	62,019
2017	1,617 (4.7)	11,236 (32.7)	7,618 (22.2)	13,199 (38.5)	652 (1.9)	34,322
Geographic region of residence at study entry						
North	735 (6.2)	5,079 (43.2)	3,448 (29.3)	2,097 (17.8)	393 (3.3)	11,752
Northeast	5,060 (5.0)	36,927 (36.7)	29,105 (28.9)	23,354 (23.2)	6,064 (6.0)	100,510
Southeast	13,522 (3.9)	97,447 (28.6)	101,323 (29.8)	110,155 (32.4)	17,834 (5.2)	340,281
South	7,448 (10.7)	22,792 (32.9)	22,139 (32.0)	12,830 (18.5)	3,929 (5.7)	69,138
Midwest	2,701 (6.4)	17,241 (40.9)	8,597 (20.4)	11,553 (27.4)	1,992 (4.7)	42,084
Diagnosis at cohort entry (ICD-10 codes)						
Paranoid schizophrenia (F20.0)	223,447 (5.3)	143,816 (32.6)	131,072 (29.7)	118,909 (26.9)	23,514 (5.3)	440,758
Hebephrenic schizophrenia (F20.1)	1,681(10.6)	5,329 (33.6)	4,098 (25.9)	3,712 (23.4)	1,014 (6.4)	15,834
Catatonic schizophrenia (F20.2)	207 (8.2)	898 (35.6)	696 (27.6)	583 (23.1)	140 (5.5)	2,524
Undifferentiated schizophrenia (F20.3)	806 (5.7)	4,370 (30.9)	3,687 (26.0)	4,452 (31.4)	840 (5.9)	14,155
Post-schizophrenic depression (F20.4)	74 (2.4)	688 (22.3)	657 (21.3)	1,510 (48.9)	159 (5.1)	3,088
Residual schizophrenia (F20.5)	1,397 (7.6)	6,369 (34.6)	4,824 (26.2)	4,320 (23.4)	1,516 (8.2)	18,426
Simple schizophrenia (F20.6)	212 (3.5)	1,786 (29.5)	2,027 (33.5)	1,693 (28.0)	327 (5.4)	6,045
Other schizophrenia (F20.8)	1,487 (2.5)	14,940 (25.7)	16,727 (28.8)	22,329 (38.5)	2,544 (4.4)	58,027
Schizoaffective disorder, manic type (F25.0)	75 (4.2)	480 (27.2)	293 (16.6)	876 (49.7)	39 (2.2)	1,763
Schizoaffective disorder, depressive type (F25.1)	28 (1.6)	419 (24.8)	308 (18.3)	874 (51.8)	57 (3.4)	1,686
Schizoaffective disorder, mixed type (F25.2)	52 (3.5)	391 (26.8)	223 (15.3)	731 (50.1)	62 (4.2)	1,459
Mean treatment duration* (SD)						
	49.94 (±38.6)	43.76 (±36.1)	38.29 (±32.6)	32.98 (±28.2)	47.04 (±37.1)	39.60 (±33.6)

*in months

Most of patients (99.9%) switched the SGA at least once during follow-up. Female sex, advanced age (> 70 years old), residence in the northeast region, study entry from 2009, and a diagnosis of schizoaffective disorders were associated with an increased risk of switching ($p<0.001$ for each variable, **Table 2**). Compared to the adjusted hazard ratio for clozapine users, the corresponding ratios for risperidone, ziprasidone, quetiapine and olanzapine users were 1.59 (95% CI, 1.57 – 1.61), 1.41 (95% CI, 1.39 – 1.44), 1.25 (95% CI, 1.23 – 1.26), and 1.11 (95% CI, 1.10 – 1.12).

The incidence of switching was 58.2/100 person-years for risperidone users, followed by 57.6/100 person-year for quetiapine users, 49.8/100 person-years for ziprasidone users, 43.5/100 person-years for olanzapine users and 37.6/100 person-years for clozapine users. Risperidone was associated with the highest risk of switching, while the corresponding risk associated with clozapine was the lowest.

Table 2: Factors associated with second generation antipsychotics switch.

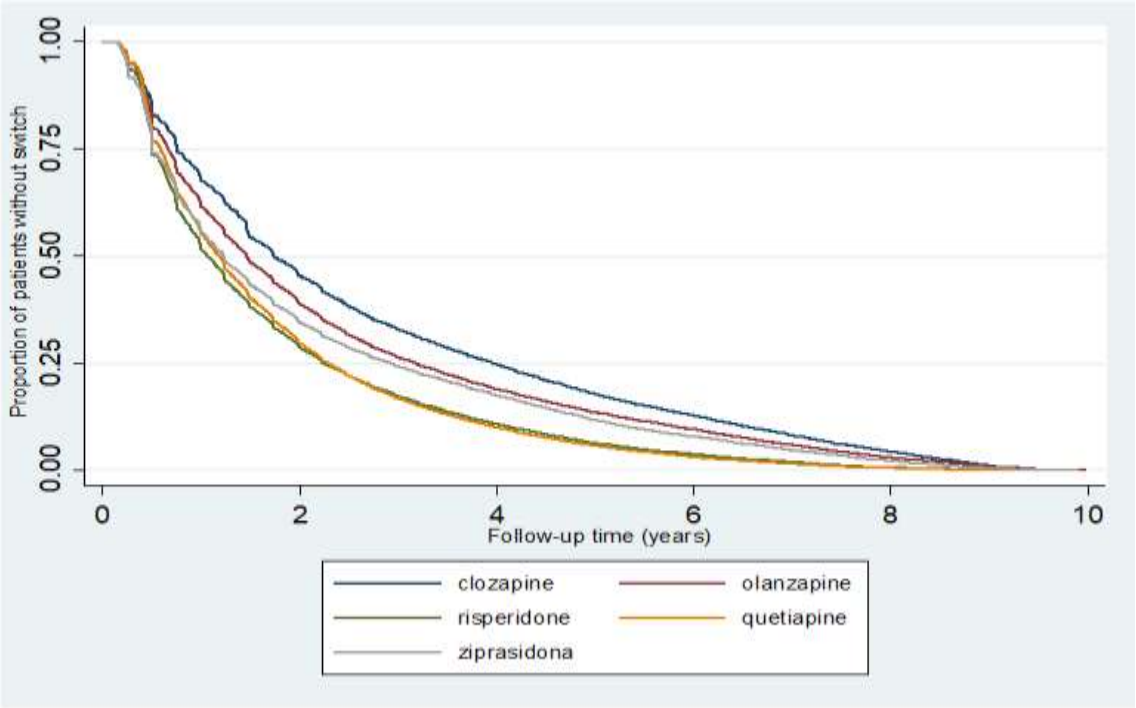
Variables	N	Incidence of switches	Hazard Ratio 95% IC not adjusted	P value	Hazard Ratio 95% IC adjusted	P value
Sex						
Males	272,879	0.48	1.00		1.00	
Females	290,886	0.53	1.10 (1.09 – 1.11)	<0.001	1.05 (1.05 – 1.06)	<0.001
Age group at study entry (years)						
18-29	115,145	0.50	1.00		1.00	
30-39	118,700	0.48	0.95 (0.94 – 0.96)	<0.001	0.94 (0.93 – 0.94)	<0.001
40-49	112,373	0.46	0.92 (0.91 – 0.93)	<0.001	0.90 (0.89 – 0.90)	<0.001
50-59	84,609	0.48	0.97 (0.96 – 0.98)	<0.001	0.89 (0.88 – 0.90)	<0.001
60-69	48,534	0.52	1.04 (1.03 – 1.06)	<0.001	0.92 (0.91 – 0.93)	<0.001
70-79	43,280	0.59	1.18 (1.17 – 1.19)	<0.001	1.03 (1.01 – 1.04)	<0.001
≥ 80	41,124	0.68	1.36 (1.34 – 1.38)	<0.001	1.14 (1.12 – 1.15)	<0.001
Year of cohort entry						
2008	125,988	0.33	1.00		1.00	
2009	49,577	0.41	1.36 (1.34 – 1.37)	<0.001	1.32 (1.31 – 1.34)	
2010	49,150	0.44	1.51 (1.49 – 1.53)	<0.001	1.45 (1.43 – 1.46)	<0.001
2011	49,877	0.45	1.58 (1.57 – 1.60)	<0.001	1.56 (1.54 – 1.57)	< 0.001
2012	41,161	0.50	1.79 (1.77 – 1.81)	<0.001	1.74 (1.72 – 1.76)	< 0.001
2013	45,106	0.54	1.97 (1.95 – 1.99)	<0.001	1.91 (1.89 – 1.93)	< 0.001
2014	46,989	0.65	2.41 (2.38 – 2.43)	<0.001	2.35 (2.32 – 2.38)	< 0.001
2015	59,576	0.74	2.77 (2.74 – 2.80)	<0.001	2.80 (2.77 – 2.83)	< 0.001
2016	62,019	0.95	3.76 (3.72 – 3.80)	<0.001	3.85 (3.81 – 3.89)	< 0.001
2017	34,322	1.86	9.59 (9.46 – 9.72)	<0.001	9.50 (9.37 – 9.63)	< 0.001
Geographic region of residence at study entry						
North	11,752	0.53	1.00		1.00	

Table 2 (continuation): Factors associated with second generation antipsychotics switch.

Variables	N	Incidence of switches	Hazard Ratio 95% IC not adjusted	P value	Hazard Ratio 95% IC adjusted	P value
Northeast	100,510	0.60	1.11 (1.09 – 1.13)	<0.001	1.04 (1.02 – 1.06)	< 0.001
Southeast	340,281	0.48	0.91 (0.89 – 0.92)	<0.001	0.88 (0.87 – 0.90)	< 0.001
South	69,138	0.47	0.85 (0.84 – 0.87)	<0.001	0.79 (0.77 – 0.80)	< 0.001
Midwest	42,084	0.50	0.93 (0.91 – 0.95)	<0.001	0.89 (0.87 – 0.91)	< 0.001
Diagnosis at study entry (ICD-10 codes)						
Paranoid schizophrenia (F20.0)	440,758	0.49	1.00		1.00	
Hebephrenic schizophrenia (F20.1)	15,834	0.47	0.94 (0.92 – 0.95)	<0.001	0.93 (0.91 – 0.94)	< 0.001
Catatonic schizophrenia (F20.2)	2,524	0.48	0.97 (0.93 – 1.00)	0.13	0.99 (0.95 – 1.03)	0.71
Undifferentiated schizophrenia (F20.3)	14,155	0.52	1.05 (1.03 – 1.07)	<0.001	0.98 (0.96 – 0.99)	0.02
Post-schizophrenic depression (F20.4)	3,088	0.50	1.00 (0.97 – 1.04)	0.64	0.95 (0.92 – 0.98)	0.01
Residual schizophrenia (F20.5)	18,426	0.44	0.89 (0.88 – 0.90)	<0.001	0.90 (0.89 – 0.92)	< 0.001
Simple schizophrenia (F20.6)	6,045	0.54	1.08 (1.05 – 1.10)	<0.001	0.99 (0.96 – 1.01)	0.56
Other schizophrenia (F20.8)	58,027	0.55	1.10 (1.09 – 1.11)	<0.001	1.01 (1.00 – 1.02)	0.001
Schizoaffective disorder, manic type (F25.0)	1,763	1.13	2.26 (2.15 – 2.36)	<0.001	1.09 (1.04 – 1.14)	< 0.001
Schizoaffective disorder, depressive type (F25.1)	1,686	1.10	2.19 (2.09 – 2.30)	<0.001	1.10 (1.05 – 1.16)	< 0.001
Schizoaffective disorder, mixed type (F25.2)	1,459	1.08	2.13 (2.02 – 2.24)	<0.001	1.11 (1.05 – 1.17)	< 0.001
SGA used at study entry						
clozapine	29,466	0.37	1.00		1.00	
olanzapine	179,486	0.43	1.15 (1.14 – 1.17)	<0.001	1.11 (1.10 – 1.12)	< 0.001
risperidone	164,612	0.58	1.58 (1.56 – 1.60)	<0.001	1.59 (1.57 – 1.61)	< 0.001
quetiapine	159,989	0.57	1.56 (1.54 – 1.58)	<0.001	1.25 (1.23 – 1.26)	< 0.001
ziprasidone	30,212	0.47	1.29 (1.27 – 1.31)	<0.001	1.41 (1.39 – 1.44)	< 0.001

Figure 2 shows the maintenance of the use of the same SGA during the follow-up period, with time without switching. Patients who used clozapine remained free from switching for a longer duration.

Figure 2: Maintenance of the use of the same antipsychotic (without switch) during the study period, Kaplan-Meier curve.



DISCUSSION

Main findings

Increased risk of SGA switching was associated with female sex, advanced age, a diagnosis of schizoaffective disorder, and type of SGA used at study entry. Risperidone users were more likely to switch to another SGA, while clozapine users were less likely to switch than other users.

Comparison with previous studies

Switching antipsychotics is a common clinical practice in schizophrenia management (Sernyak et al., 2005; Kreyenbuhl et al., 2007; Nyhuis et al., 2010). Our findings confirmed this, and we found that the switches happened at least once in 10 years. The SGAs are similar in terms of effectiveness, except clozapine, but show

significant differences in the tolerability profile and adverse reactions, which may explain the switch (Siskind et al., 2016; Preda and Bora, 2019).

Women were more likely to switch SGAs than were men. This finding is consistent with that in other studies (Barbui et al., 2005; Nyhuis et al., 2010) and could be attributed to sex differences and to the fact that women use more health services than do men and, in turn, could detect a suboptimal treatment response or serious adverse event early (Lindamer et al., 2003). There are sex differences in the tolerability and maintenance regimens of antipsychotics in patients with schizophrenia (Seeman, 2004; Barbui et al., 2005; Leotsakou, 2008). Women are less tolerant than men to antipsychotics (Barbui et al., 2005). Furthermore, women tend to report adverse effects, such as extrapyramidal and anticholinergic reactions, hyperprolactinemia, and weight gain, more frequently, whereas men report more sexual problems (Barbui et al., 2005; Schwartz et al., 2015; Alberich et al., 2019). Women and men could not be considered a homogenous group in the use of antipsychotics (Seeman, 2004).

Advanced age was another factor associated with switching, which conflicts with other findings. The age of the patients was not a significant predictor in other studies, and the age group of switchers was between 42 and 55 years (Kreyenbuhl et al., 2007; Nyhuis et al., 2010). Another study showed that advanced age reduced the likelihood of switching overall (Sernyak et al., 2005).

Residents of the northeast region of Brazil were more likely to switch SGAs, which may reflect of socioeconomic factors. The northeast region is one of the poorest regions in Brazil, with high rates of unemployment, illiteracy, and poor basic sanitation. It succeeds the southeastern part in the number of schizophrenia cases in Brazil and is considered a vulnerable region in terms of the development of this disease, and treatment gaps and non-adherence (Dornelas, 2019). Although the country offers universal coverage, there is a shortage of doctors and specialized health professionals in certain regions (Oliveira et al., 2017). as well as a lack of availability of medicines, with the northeast and northern regions being the most affected. Inadequate availability of psychiatrists and nurses in mental health facilities are considered a significant predictor of treatment gap (Lora, 2012).

The subtypes of schizophrenia are generally not studied separately and studies involving patients with schizophrenia also include patients with schizoaffective disorder (BRAZIL, 2014; Leposavic et al., 2015; Mattila et al., 2015). Although it did not seem predictor of treatment response (Mattila et al., 2015), a diagnosis of schizoaffective

disorders, compared to that of paranoid schizophrenia, was likely to associated with SGA switching, as found in our study. Although relevant data are scarce and evidences pertaining to schizophrenia also includes evidence pertaining to schizoaffective disorders, the effectiveness and tolerability profile of SGAs may differ across these conditions (Murru et al., 2016).

The use of risperidone was associated with a higher risk to switching in our cohort. Despite widespread use, low price, and no clear differences in effectiveness compared to those of other SGAs risperidone produces more movement disorders and prolactin increase than do other SGAs (Komossa et al., 2011). In a study conducted among schizophrenia outpatients, in 37 countries (n=17,000 patients) in which the switches from risperidone to olanzapine and vice versa were compared, patients who switched from risperidone to olanzapine exhibited more favorable outcomes and remained on the medication longer (Hong et al., 2012). In another systematic review (15 studies, n= 7760 patients), a comparison between SGAs showed that risperidone was slightly less acceptable than olanzapine (Komossa et al., 2011).

Patients using clozapine switched less than did patients using other SGAs. Meta-analyses have shown that clozapine is more effective than other SGAs, being superior for positive symptoms in the short and long term (Asenjo Lobos et al., 2010; Siskind et al., 2016). Regarding negative symptoms, clozapine was superior only in the short term (Siskind et al., 2016). A cohort study conducted in Sweden among patients (n=26046) diagnosed with schizophrenia and using antipsychotics showed that clozapine users were most likely to refill prescriptions and had lower rates of re-hospitalization and death by suicide (Ringback Weitoft et al., 2014). Other studies also highlighted that the adherence rate was significantly higher in patients treated with clozapine (Cooper et al., 2007; Ascher-Svanum H, 2008). These significant clinical benefits may have contributed to clozapine users switching less than other SGA users in our cohort.

However, clozapine is used less frequently and later in treatment. Studies have shown that there are long delays in starting treatment with clozapine in resistant patients (Wheeler, 2008; Howes et al., 2012; Alessi-Severini et al., 2013). Guidelines for schizophrenia treatment do not recommend clozapine as the first option (Brazil, 2013; Kuipers, 2014; Remington et al., 2017; Preda and Bora, 2019). It is offered only to patients who have not responded adequately to adequate doses of at least two different antipsychotics. This is probably due to the risk of inducing agranulocytosis

(almost 1%), which can be fatal, and the need for closer monitoring (Preda and Bora, 2019; Van Zuuren, 2019). Other concerns include the risk of cardiovascular diseases. To ensure a balance between effectiveness and safety and considering real-world information about the use of clozapine in outpatients, guidelines could be reviewed and different recommendations could be made.

Strengths and limitations of the study

This is the first national cohort study that assessed the factors associated with switching of SGAs dispensed by the Brazilian public sector over 10 years. The use of a nationwide pharmaceutical database allowed us to investigate a large quantity of data on the use of antipsychotics in real-life and to obtain a representative and very large patient population with schizophrenia.

There are some limitations of this study. First, despite the reliability of the data, the diagnoses were not validated. Second, SIA/SUS is an administrative database that does not consider dispensation from private pharmacies, which could lead to an underestimation of the use of these antipsychotics. Nevertheless, APAC/SIA covers more than 70% of the Brazilian population (more than 148 million inhabitants). Third, as an administrative database, it is not intended for research purposes and may have system data feed errors. However, we carefully checked data inconsistencies to avoid this type of bias and excluded patients who received antipsychotics only once or for less than 90 days. Fourth, detailed clinical data as well as the reasons that determined the switches are unavailable because the original purpose of this database is to register the consumption, the charge, and the payment of dispensing high-cost medicines.

CONCLUSION

This nationwide cohort study elucidated the factors associated with SGAs switching in a real-world setting. The choice of the prescribed antipsychotic can determine the trend for switching and affect the long and short-term outcomes for patients with life-long disorders. The findings of our study have implications for future research.

DECLARATIONS:

Ethics statement: The study used only secondary data from unrestricted access, obtained from DATASUS, therefore it is exempt from the need for submission to Ethics Council as sole paragraph of Resolution of the National Health Council No. 510/2016.

Funding: This study was funded by FAPESP, grants 2017/20668-7. FAPESP had no role in the study design, collection, analysis or interpretation of the data, writing the manuscript, or the decision to submit the paper for publication.

Contributors: IF and LCL were responsible for the study concept and design. MTS and IF extracted the data and performed the statistical analysis. IF and LCL drafted the manuscript. All authors were responsible for critical revision of the manuscript and have accepted the final version.

REFERENCES

Alberich, S., Fernández-Sevillano, J., González-Ortega, I., Usall, J., Sáenz, M., González-Fraile, E., and González-Pinto, A. (2019). A systematic review of sex-based differences in effectiveness and adverse effects of clozapine. Psychiatry Res 280**,** 112506.

Alessi-Severini, S., Le Dorze, J.A., Nguyen, D., Honcharik, P., and Eleff, M. (2013). Clozapine prescribing in a Canadian outpatient population. PLoS One 8**,** e83539.

Ascher-Svanum H, Z.B., Faries De, Lacro Jp, Dolder Cr, Peng X (2008). Adherence and persistence to typical and atypical antipsychotics in the naturalistic treatment of patients with schizophrenia. Patient Prefer Adherence 2**,** 67-77.

Asenjo Lobos, C., Komossa, K., Rummel-Kluge, C., Hunger, H., Schmid, F., Schwarz, S., and Leucht, S. (2010). Clozapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev**,** Cd006633.

Barbosa, W.B., Costa, J.O., De Lemos, L.L.P., Gomes, R.M., De Oliveira, H.N., Ruas, C.M., Acurcio, F.A., Barbui, C., Bennie, M., Godman, B., and Guerra, A.A., Jr. (2018). Costs in the Treatment of Schizophrenia in Adults Receiving Atypical Antipsychotics: An 11-Year Cohort in Brazil. Appl Health Econ Health Policy 16**,** 697-709.

Barbui, C., Nosè, M., Bindman, J., Schene, A., Becker, T., Mazzi, M.A., Kikkert, M., Camara, J., Born, A., and Tansella, M. (2005). Sex differences in the subjective tolerability of antipsychotic drugs. J Clin Psychopharmacol 25**,** 521-526.

Bernardo, M., Vieta, E., Saiz Ruiz, J., Rico-Villademoros, F., Alamo, C., and Bobes, J. (2011). Recommendations for switching antipsychotics. A position statement of the Spanish Society of Psychiatry and the Spanish Society of Biological Psychiatry. Rev Psiquiatr Salud Ment 4**,** 150-168.

Brazil (2008). Rede Interagencial de Informação para a Saúde. Indicadores básicos para a saúde no Brasil: conceitos e aplicações / Rede Interagencial de Informação para a Saúde Brasília: Ripsa.

Brazil. (2013). Protocolo clínico e diretrizes terapêuticas. Esquizofrenia. 2013. http://portalarquivos.saude.gov.br/images/pdf/2014/abril/02/pcdt-esquizofrenia-livro-2013.pdf [Accessed Nov 12, 2019].

Brazil. (2014). Protocolo clínico e diretrizes clínicas. Transtorno Esquizoafetivo. http://conitec.gov.br/images/Protocolos/TranstornoEsquizoafetivo.pdf [Accessed Nov 12, 2019].

Buckley, P.F., and Correll, C.U. (2008). Strategies for dosing and switching antipsychotics for optimal clinical management. J Clin Psychiatry 69 Suppl 1**,** 4-17.

Cerovecki, A., Musil, R., Klimke, A., Seemüller, F., Haen, E., Schennach, R., Kühn, K.U., Volz, H.P., and Riedel, M. (2013). Withdrawal symptoms and rebound syndromes associated with switching and discontinuing atypical antipsychotics: theoretical background and practical recommendations. CNS Drugs 27**,** 545-572.

Cooper, D., Moisan, J., and Grégoire, J.P. (2007). Adherence to atypical antipsychotic treatment among newly treated patients: a population-based study in schizophrenia. J Clin Psychiatry 68**,** 818-825.

Correll, C.U. (2010). From receptor pharmacology to improved outcomes: individualising the selection, dosing, and switching of antipsychotics. Eur Psychiatry 25 Suppl 2**,** S12-21.

Dornelas, L.T.S.D., L. H. S.; Dornelas, C. R. S.; De Melo, G. F.; Souza, N. B.; Faria, T. A. V. (2019). Fatores socioeconomicos e esquizofrenia nas regioes brasileiras. Revista Científica Online 11**,** 8p.

Faries, D.E., Ascher-Svanum, H., Nyhuis, A.W., and Kinon, B.J. (2009). Clinical and economic ramifications of switching antipsychotics in the treatment of schizophrenia. BMC Psychiatry 9**,** 54.

Ganguli, R. (2002). Rationale and strategies for switching antipsychotics. Am J Health Syst Pharm 59**,** S22-26.

Hong, J., Novick, D., Brugnoli, R., Karagianis, J., Dossenbach, M., and Haro, J.M. (2012). Clinical consequences of switching from olanzapine to risperidone and vice versa in outpatients with schizophrenia: 36-month results from the Worldwide Schizophrenia Outpatients Health Outcomes (W-SOHO) study. BMC Psychiatry 12**,** 218.

Howes, O.D., Vergunst, F., Gee, S., Mcguire, P., Kapur, S., and Taylor, D. (2012). Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. Br J Psychiatry 201**,** 481-485.

Keks, N., Schwartz, D., and Hope, J. (2019). Stopping and switching antipsychotic drugs. Aust Prescr 42**,** 152-157.

Komossa, K., Rummel-Kluge, C., Schwarz, S., Schmid, F., Hunger, H., Kissling, W., and Leucht, S. (2011). Risperidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev**,** Cd006626.

Kreyenbuhl, J., Marcus, S.C., West, J.C., Wilk, J., and Olfson, M. (2007). Adding or switching antipsychotic medications in treatment-refractory schizophrenia. Psychiatr Serv 58**,** 983-990.

Kuipers, E.E.A. (2014). Psychosis and schizophrenia in adults. Treatment and management. The Nice guideline on treatment and management. London: National Institute for Health and Care Excellence (UK); 2014.

Leotsakou, C., Sardis, A. & Paterakis, P. (2008). Sex differences in side effects of second-generation antipsychotics. Ann Gen Psychiatry 7**,** S106.

Leposavic, L., Leposavic, I., Saula-Marojevic, B., and Gavrilovic, P. (2015). Paranoid Schizophrenia versus Schizoaffective Disorder: Neuropsychological Aspects. Srp Arh Celok Lek 143**,** 391-396.

Lindamer, L.A., Bailey, A., Hawthorne, W., Folsom, D.P., Gilmer, T.P., Garcia, P., Hough, R.L., and Jeste, D.V. (2003). Gender differences in characteristics and service use of public mental health patients with schizophrenia. Psychiatr Serv 54**,** 1407-1409.

Lindner, L.M., Marasciulo, A.C., Farias, M.R., and Grohs, G.E.M. (2009). Avaliação econômica do tratamento da esquizofrenia com antipsicóticos no Sistema Único de Saúde. Revista de Saúde Pública 43**,** 62-69.

Lora, A., Kohn, Robert, Levav, Itzhak, Mcbain, Ryan, Morris, Jodi. Et Al. (2012). Service availability and utilization and treatment gap for schizophrenic disorders: a survey in 50 low- and middle-income countries. Bulletin of the World Health Organization 90**,** 47-54B.

Mattila, T., Koeter, M., Wohlfarth, T., Storosum, J., Van Den Brink, W., De Haan, L., Derks, E., Leufkens, H., and Denys, D. (2015). Impact of DSM-5 changes on the diagnosis and acute treatment of schizophrenia. Schizophr Bull 41**,** 637-643.

Murru, A., Hidalgo, D., Bernardo, M., Bobes, J., Saiz-Ruiz, J., Álamo, C., and Vieta, E. (2016). Antipsychotic switching in schizoaffective disorder: A systematic review. World J Biol Psychiatry 17**,** 495-513.

Nyhuis, A.W., Faries, D.E., Ascher-Svanum, H., Stauffer, V.L., and Kinon, B.J. (2010). Predictors of switching antipsychotic medications in the treatment of schizophrenia. BMC Psychiatry 10**,** 75.

Oliveira, A.P.C.D., Gabriel, M., Poz, M.R.D., and Dussault, G. (2017). Desafios para assegurar a disponibilidade e acessibilidade à assistência médica no Sistema Único de Saúde %J Ciência & Saúde Coletiva. 22**,** 1165-1180.

Preda, A., and Bora, R.G. (2019). Esquizofrenia. BMJ Best Practice. https://bestpractice-bmj-com.libaccess.lib.mcmaster.ca/topics/en-gb/406/pdf/406.pdf (Accessed Nov 12, 2019).

Remington, G., Addington, D., Honer, W., Ismail, Z., Raedler, T., and Teehan, M. (2017). Guidelines for the Pharmacotherapy of Schizophrenia in Adults. Can J Psychiatry 62**,** 604-616.

Ringback Weitoft, G., Berglund, M., Lindstrom, E.A., Nilsson, M., Salmi, P., and Rosen, M. (2014). Mortality, attempted suicide, re-hospitalisation and prescription refill for clozapine and other antipsychotics in Sweden-a register-based study. Pharmacoepidemiol Drug Saf 23**,** 290-298.

Santos, A.S.G., Isabella Piassi; Vidal, Carlos Eduardo Leal; Ruas, Cristina Mariano (2017). Economic evaluation of antipsychotics for the treatment of schizophrenia: a systematic review. J Bras Econ Saúde 9**,** 207-228.

Schwartz, E., Charlotte, M., Slade, E., Medoff, D., Li, L., Dixon, L., Kilbourne, A., and Kreyenbuhl, J. (2015). Gender differences in antipsychotics prescribed to veterans with serious mental illness. Gen Hosp Psychiatry 37**,** 347-351.

Seeman, M.V. (2004). Gender differences in the prescribing of antipsychotic drugs. Am J Psychiatry 161**,** 1324-1333.

Sernyak, M.J., Leslie, D., and Rosenheck, R. (2005). Predictors of antipsychotic medication change. J Behav Health Serv Res 32**,** 85-94.

Siskind, D., Mccartney, L., Goldschlager, R., and Kisely, S. (2016). Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry 209**,** 385-392.

Stroup, T.S., and Gray, N. (2018). Management of common adverse effects of antipsychotic medications. World Psychiatry 17**,** 341-356.

Van Zuuren, E.J. (2019). Schizophrenia. 2019. https://www.dynamed.com/condition/schizophrenia [Accessed Nov 12, 2019}.

Wheeler, A.J. (2008). Treatment pathway and patterns of clozapine prescribing for schizophrenia in New Zealand. Ann Pharmacother 42**,** 852-860.

Xu, L., and Krishnaswamy, S. (2018). Switch-associated adverse events: focus on olanzapine. Australas Psychiatry 26**,** 635-639.

5.2.2 Artigo científico 4 – Sex differences in the use of atypical antipsychotics in early-onset schizophrenia: a nationwide population-based study in Brazil

O artigo científico *"Sex differences in the use of atypical antipsychotics in early-onset schizophrenia: a nationwide population-based study in Brazil"* teve como objetivo investigar a diferença de sexo no uso de antipsicóticos atípicos para tratamento de esquizofrenia em crianças e adolescentes.

A formatação seguiu as regras da revista *BMC Psychiatric* e foi submetido em 22/12/2020. Encontra-se em fase de revisão.

Revista: *BMC Psychiatric*
ISSN: 1471-244X
Versão online: 1471-244X
Fator de impacto: 2,7
Classificação Webqualis/Capes, área de Farmácia, 2020: A3

Comprovante de submissão encontra-se no **Anexo F.**

Sex differences in the use of atypical antipsychotics in early-onset schizophrenia: a nationwide population-based study in Brazil

Izabela Fulone[1]
Pharmaceutical Sciences Graduate Course, University of Sorocaba, UNISO, Sorocaba, Brazil
E-mail: bela.fulone@gmail.com;

Marcus Tolentino Silva[1]
Pharmaceutical Sciences Graduate Course, University of Sorocaba, UNISO, Sorocaba, Brazil
E-mail: marcusts@gmail.com

Luciane Cruz Lopes[1*]
Pharmaceutical Sciences Graduate Course, University of Sorocaba, UNISO, Sorocaba, Brazil
E-mail: luslopesbr@gmail.com; luciane.lopes@prof.uniso.br

***Corresponding author: Luciane Cruz Lopes**
Pharmaceutical Sciences Graduate Course, University of Sorocaba, UNISO, Sorocaba, Brazil
Rodovia Raposo Tavares, KM 92,5 - Sorocaba, São Paulo, Brazil
ZIP Code: 18023-000 24
Phone: 55 19 99781-8441 Fax: 55 15 2101-7074

Disclosure: No conflict of interest.

Financial support: São Paulo Research Foundation (Fapesp) grants 2017/20668-7

Word count:2802

Number of references: 38

Number of figures: 2

Number of tables: 3

Supplementary materials: 0

ABSTRACT

Backgroud: The use of atypical antipsychotics for the treatment of schizophrenia and other mental disorders in populations under 18 years of age is increasing worldwide. Little is known about treatment patterns and the influence of sex differences, which may be a predictor of clinical outcomes.

Objective: We aimed to investigate sex differences in the use of atypical antipsychotics in patients with early-onset schizophrenia (EOS) assisted by the public health system in Brazil.

Methods: We conducted a cross-sectional study of outpatients with EOS aged 10 to 17 years who received at least one provision of atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine or ziprasidone) from a large Brazilian pharmaceutical assistance programme. Data were retrieved from a nationwide administrative database from 2008 - 2017.

Results: Of the 49,943 patients with EOS, 63.5% were males, and the mean age was 13.6 years old. The patients were using risperidone (62.5%), olanzapine (19.6%), quetiapine (12.4%), ziprasidone (3.3%) and clozapine (2.2%). We found sex differences, especially in the 13-17 year age group (65.1% for males vs. 34.9% for females, $p<0.001$), in the use of risperidone (72.1% for males vs. 27.9% for females, $p<0.001$) and olanzapine (66.5% for males vs. 33.5% for females, $p<0.001$). Only in the 13 to 17 years age group were the prescribed doses of olanzapine ($p=0.012$) and quetiapine ($p=0.041$) slightly higher for males than for females.

Conclusion: Our findings showed sex differences among patients diagnosed with EOS and who received atypical antipsychotics. More attention should be devoted to sex differences in research and clinical practice.

Keywords: schizophrenia; child; adolescent; antipsychotic agents; sex difference;

Background

Early-onset schizophrenia is defined as schizophrenia diagnosed before 18 years old. The differential diagnosis is difficult, and approximately 30 to 50% of patients with affective or other atypical psychotic symptoms are misdiagnosed with early-onset schizophrenia [1].

The prevalence of psychotic disorders in the 10 to 18 years age group is relatively low (approximately 0.4%) [2]. The onset of schizophrenia prior to age 13 years is rarer, affecting 1.6 to 1.9 per 100,000 child population, but between the ages of 13 and 17 years old, the prevalence increases more rapidly [3].

The frequency and duration of psychotic episodes could have deleterious neuropsychological, neurophysiological, and neurostructural effects, particularly in children and adolescents [1]. For this reason, it is important to optimize early diagnosis and start an appropriate treatment to improve outcomes [4].

Many studies have reported sex differences, which highlights the association between male sex and earlier age of onset schizophrenia [2, 5, 6]. Male schizophrenia patients tend to show an earlier age of onset, more negative symptoms, higher relapse rate, poor outcomes and worse responses to antipsychotics than female schizophrenic patients [6]. Other studies have not endorsed the sex difference and showed controversial results or no significant differences between males and females [4, 7, 8].

Pharmacological treatment in this age group is challenging from both a clinical and ethical perspective [9]. There are few studies and limited data based on evidence that supports the effectiveness, safety, and effects of long-term antipsychotic (typic and atypical) use in children and adolescents, as it is a rare disorder and is difficult to conduct trials in this group age [10]. In recent years, there has been no significant increase in the number of trials addressing it with this particular age group [11].

However, antipsychotics have long been seen as playing a key role in the treatment of schizophrenia in children and adolescents [9, 12]. There is no convincing evidence about the superiority of atypical antipsychotics over typical antipsychotics, but atypical antipsychotics have been considered the first line of pharmacological treatment in EOS due to the lower incidence of adverse reactions and extrapyramidal symptoms and are more acceptable than typical antipsychotics [10].

Most of the recommendations shown in the guidelines for the treatment of schizophrenia in children and adolescents are extrapolations of existing guidelines for

adults due to the lack of specific evidence about this age range [9, 13, 14]. Many antipsychotics are not product licenced for use in children and/or adolescents, and prescribers and parents should be aware and responsible for their use [9, 15, 16].

However, studies have reported an increase in the use of antipsychotics in this group age and an increase in the incidence of early-onset schizophrenia and other mental disorders in recent years [4, 8, 17]. Part of this marked increase can be attributed to off-label use to treat behaviour disorders, attention deficit, hyperactivity, and anxiety disorders [17, 18].

There are still important gaps in evidence regarding sex differences and the treatment of mental disorders and in this vulnerable population under 17 years old [11, 17]. The profile of children and adolescent users of antipsychotics with early-onset schizophrenia is still controversial, and little is known about their treatment patterns in the real world, thus indicating the need for further study. The aim of this study was to investigate potential sex differences in the use of atypical antipsychotics among patients with early-onset schizophrenia.

Method

Study design

This was a cross-sectional study using records from the national ambulatory administrative database, Ambulatory Information System, SIA/SUS.

Setting

The national administrative database Ambulatory Information System (SIA) of the Unified Health System (SUS), contains information about all procedures for outpatient care and dispensing of high-cost medicines for certain diseases according to Brazilian guidelines. This database is managed by the Ministry of Health and registers over 200 million procedures/month [19]. It has unrestricted access, and the individualized data have been publicly available since 2008.

Atypical antipsychotics are considered high-cost medicines in Brazil, and the following medications are provided by SUS: oral clozapine, olanzapine, quetiapine, risperidone and ziprasidone. Injectable atypical antipsychotics are not available. These drugs are dispensed to patients only after analysing the request and determining whether the request is in compliance with Brazilian guidelines for the treatment of

schizophrenia in adults. Then, atypical antipsychotics are provided to patients monthly for a period of 3 months, and the quantity prescribed could cover only a maximum duration of 90 days. After this period, a new request and analysis are necessary according to the rules in Brazil.

There are no specific national guidelines for the treatment of schizophrenia in children and adolescents. Clinicians use the guidelines for adults as a reference. Brazilian guidelines for the treatment of schizophrenia in adults recommend atypical antipsychotic monotherapy and the use of clozapine only in cases in which patients are refractory to at least two other antipsychotics [20].

Participants

We included all patients aged 10 to 17 years old who were diagnosed with schizophrenia according to the International Classification of Diseases, tenth Revision, Clinical Modification (ICD-10) and received at least one prescription of atypical antipsychotics through a pharmaceutical assistance programme from the SUS between 2008 and 2017.

Variables

We compared sex differences in the demographic and clinical characteristics of the study participants, and they were classified by sex for further analysis. The baseline demographic variables considered were sex, age at study entry, race, geographic region of residence at study entry, and year of study entry (defined as the year of the first provision of atypical antipsychotics from January 1, 2008, to December 31, 2017). The baseline clinical variables considered were diagnosis according to ICD-10 at study entry (paranoid schizophrenia or other types) and type of atypical antipsychotic used at study entry.

Measurement

The mean dose of the antipsychotics used was investigated according to the age group (10-12 years and 13-17 years) and compared by sex differences. We calculated the mean dose and defined daily dose (DDD) ratios to make comparisons between five types of antipsychotics available in the SUS. The DDD is a standardized unit of measurement in pharmacological studies, defined by the average maintenance dose of a drug in adults and allows the comparison of drug use/consumption from

different countries or between population groups [21]. The DDDs of the investigated oral antipsychotics are clozapine (300.0 mg), olanzapine (10.0 mg), risperidone (5.0 mg), quetiapine (400.0 mg), and ziprasidone (80.0 mg) [21].

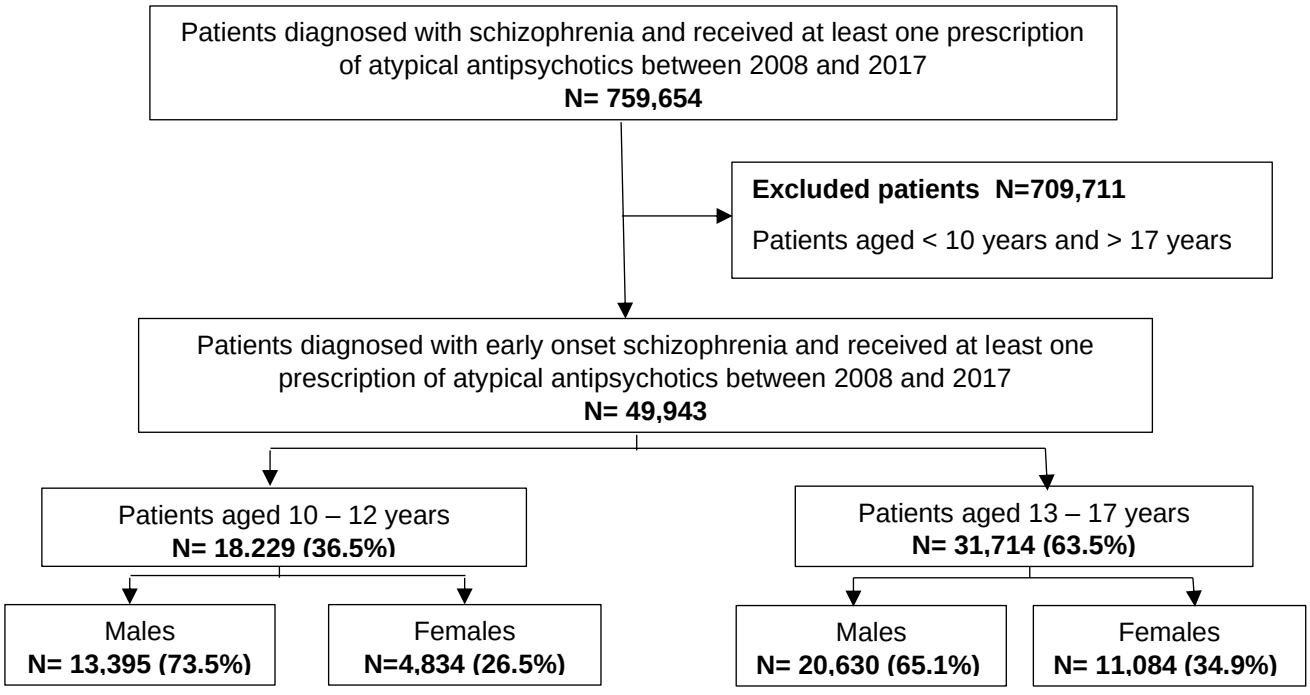
Statistical analysis

Initially, the characteristics of the patients were described and stratified by sex. Then, we calculated the Pearson chi-squared tests or independent sample t-tests to investigate the differences in demographic and clinical characteristics between male and female groups. The doses were described by means and standard deviations. The ratio mean dose/defined daily dose (DDD) was calculated to normalize the doses and make comparisons. The rate of antipsychotic use per year was defined by percentage and plotted on a graph to show the trend of use over the years of the study. A significance level of $P < 0.05$ and a confidence interval of 95% were adopted.

RESULTS

We identified 49,943 patients aged 10-17 years who were diagnosed with schizophrenia and who received at least one provision of atypical antipsychotics by the SUS from 2008 to 2017 (**Figure 1)**.

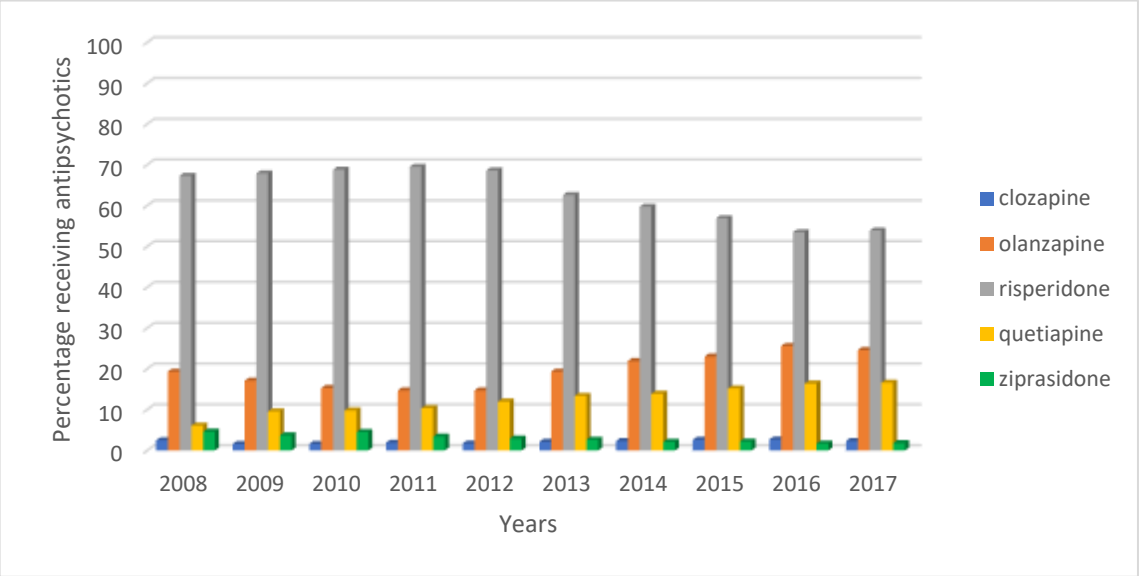
Figure 1: Flow chart of study.



The most of patients were males (63.5%), with mean age 13.6 (±2.5) years old, lived in the southeast of Brazil (57.7%), diagnosed with paranoid schizophrenia (71.8%), and used at study entry mainly risperidone (62.5%), olanzapine (19.6%), quetiapine (12.4%), ziprasidone (3.3%) and clozapine (2.2%).

Figure 2 shows the trend of use of atypical antipsychotics over ten years of study. For the years 2008 to 2017, risperidone was the most prescribed atypical antipsychotic, reaching rates above 53.0%. Olanzapine was the second most common antipsychotic prescribed. The use trend of quetiapine and olanzapine increased especially from 2013.

Figure 2: The percentage of children and adolescents receiving atypical antipsychotic over the period 2008–2017.



The sex difference is highlighted especially in the group age of 13-17 years old ($p<0.001$), residents in the southeast and south region ($p<0.001$) of Brazil and who used risperidone at study entry ($p<0.001$), with male predominance (**Table 1).** There was no sex difference in the use of clozapine.

The year at study entry did not differ significantly between sex over 10 years. Race and type of schizophrenia also did not differ between sex.

Table 1: Demographic and clinical characteristics of patients with early-onset schizophrenia by sex from 2008 to 2017 in Brazil.

Variables	Overall N=49,943	Male N=34,025	Female N=15,918	P
Demographic characteristics				
Age at study entry (years)				
10-12	18,229	13,395 (73.5)	4,834 (26.5)	<0.001
13 to 17 years	31,714	20,630 (65.1)	11,084 (34.9)	
Mean age (SD)				
	13.6 (±2.5)	13.45 (±2.5)	13.91 (±2.4)	<0.001
Race				
White	6,096	4,137 (67.9)	1,959 (32.1)	0.451
Black	579	404 (69.8)	175 (30.2)	
Pardo	4,154	2,795 (67.3)	1,359 (32.7)	
Yellow	1,073	733 (68.3)	340 (31.7)	
Indigenous	26	21 (80.7)	5 (19.3)	
No information	38,015	25,935 (68.2)	12,080 (31.8)	
Year of study entry				
2008	8,272	5,710 (69.1)	2,562 (30.9)	0.113
2009	4,341	2,899 (66.8)	1,442 (33.2)	
2010	4,654	3,188 (68.5)	1,466 (31.5)	
2011	4,711	3,198 (67.9)	1,513 (32.1)	
2012	4,156	2,812 (67.6)	1,344 (32.3)	
2013	4,380	2,929 (66.9)	1,451 (33.1)	
2014	4,582	3,148 (68.7)	1,434 (31.3)	
2015	5,191	3,575 (68.9)	1,616 (31.1)	
2016	5,108	3,501 (68.5)	1,607 (31.5)	
2017	4,548	3,065 (67.4)	1,483 (32.6)	
Geographic region of residence at study entry				
North	1,319	840 (63.7)	479 (36.3)	<0.001
Northeast	10,244	6,858 (66.9)	3,386 (33.1)	
Southeast	28,835	19,703 (68.3)	9,132 (31.7)	
South	6,645	4,679 (70.4)	1,966 (29.6)	
Midwest	2,900	1,945 (67.1)	955 (32.9)	
Clinical characteristics				
Diagnosis at study entry				
Paranoid schizophrenia	35,887	24,394 (67.9)	11,493 (32.1)	0.240
Other types of schizophrenia	14,056	9,631 (68.5)	4,425 (31.5)	
Atypical antipsychotics used at study entry				
clozapine	1,092	731 (66.9)	361 (33.1)	0.395
olanzapine	9,799	6,511 (66.5)	3,288 (33.5)	<0.001
risperidone	31,193	22,497 (72.1)	8,696 (27.9)	<0.001
quetiapine	6,183	3,357 (54.3)	2,826 (45.7)	<0.001
ziprasidone	1,665	919 (55.2)	746 (44.8)	<0.001

Table 2 shows the doses prescribed to patients aged 10 – 12 years. There were no significant sex differences in the dosing of atypical antipsychotics prescribed in this age range. The ratio of mean dose/DDD was lower than 0.54, which is lower than DDD in adults.

Table 2: Antipsychotic prescription and their mean dose for patients age 10-12 years with early-onset schizophrenia.

Variables	Overall N= 18,229	Male N= 13,395	Female N= 4,834	P
Atypical antipsychotic				
clozapine (N)	(199)	(138)	(61)	
Dose (mg/day)	150.82 ± 138.79	144.49 ± 138.15	165.13 ± 140.31	0.334
Mean dose/DDD ratio	0.502 ± 0.46	0.481 ± 0.46	0.55 ±0.46	
olanzapine (N)	(1,850)	(1,316)	(534)	
Dose (mg/day)	5.18 ± 15.1	5.43 ± 17.72	4.56 ± 3.82	0.261
Mean dose /DDD ratio	0.512 ± 1.51	0.54 ± 1.77	0.45 ± 0.38	
risperidone (N)	(14,338)	(10,769)	(3,569)	
Dose (mg/day)	1.19 ± 2.11	1.19 ± 1.83	1.21 ± 2.79	0.501
Mean dose /DDD ratio	0.24 ± 0.42	0.24 ± 0.36	0.24 ± 0.55	
quetiapine (N)	(1,404)	(899)	(505)	
Dose (mg/day)	81.22 ± 109.02	85.06 ± 116.13	74.37 ± 94.78	0.077
Mean dose /DDD ratio	0.20 ± 0.27	0.21 ± 0.29	0.18 ± 0.23	
ziprasidone (N)	(419)	(257)	(162)	
Dose (mg/day)	43.43 ± 33.61	43.11 ± 33.36	43.94 ± 34.10	0.805
Mean dose /DDD ratio	0.54 ± 0.42	0.53 ± 0.42	0.54 ± 0.42	

Table 3 shows the doses prescribed to patients aged 13 – 17 years. There were sex differences in the dosing of olanzapine (5.60 mg/day for males, 5.09 mg/day for females, p=0.012) and quetiapine (114.87 mg/day for males, 100.28 mg/day for females, p=0.041), such that males received slightly higher doses of olanzapine and quetiapine than females aged 13 to 17 years old. Considering the rate mean dose/DDD, we observed that prescribed doses were lower than DDD, which is lower than 0.76 in adults.

Table 3: Antipsychotic prescription and their mean dose for patients age 13-17 years with early-onset schizophrenia.

Variables	Overall N=31,714	Male N= 20,630	Female N= 11,084	P
Atypical antipsychotic				
clozapine (N)	(892)	(592)	(300)	
Dose (mg/day)	184.45 ± 338.72	178.88 ± 166.22	195.43 ± 535.82	0.490
Mean dose/DDD ratio	0.61 ± 1.12	0.59 ± 0.55	0.65 ± 1.78	
olanzapine (N)	(7,939)	(5,186)	(2,753)	
Dose (mg/day)	5.42 ± 8.57	5.60 ± 9.85	5.09 ± 5.35	0.012
Mean dose /DDD ratio	0.54 ± 0.85	0.56 ± 0.98	0.51 ± 0.53	
risperidone (N)	(16,823)	(11,705)	(5,118)	
Dose (mg/day)	1.42 ± 2.66	1.44 ± 2.40	1.37 ± 3.18	0.093
Mean dose /DDD ratio	0.28 ± 0.53	0.29 ± 0.48	0.27 ± 0.63	
quetiapine (N)	(44,775)	(2,455)	(2,320)	
Dose (mg/day)	107.78 ± 247.59	114.87 ± 327.43	100.28 ± 112.41	0.041
Mean dose /DDD ratio	0.26 ± 0.62	0.28 ± 0.82	0.25 ± 0.28	

Table 3 (continuation): Antipsychotic prescription and their mean dose for patients age 13-17 years with early-onset schizophrenia.

Variables	Overall N=31,714	Male N= 20,630	Female N= 11,084	P
ziprasidone (N)	(1,245)	(662)	(583)	
Dose (mg/day)	61.10 ± 131.82	65.41 ± 148.99	56.22 ± 109.02	0.220
Mean dose /DDD ratio	0.76 ± 1.64	0.81 ± 1.86	0.70 ± 1.36	

DISCUSSION

Main findings

Our findings highlighted the outpatient use of atypical antipsychotics by sex in a large and representative population of children and adolescents assisted by the public health system in Brazil. The most commonly prescribed atypical antipsychotic among children and adolescents was risperidone, followed by olanzapine. Sex differences were observed, especially in the 12-17 years age group and in the choice of atypical antipsychotics prescribed, such as risperidone and olanzapine, with significant male predominance. The prescribed doses of olanzapine and quetiapine were slightly higher among males aged 13-17 years than among females.

Comparison with previous studies

The onset of mental disorders, including schizophrenia and other psychotic disorders, commonly occurs in adolescence due to important changes in the brain structure with complex interactions among biological, psychological and social factors [10]. Most of the antipsychotic users identified in this study with a diagnosis of schizophrenia were adolescents in the age range 13-17 years, consistent with other studies from Canada, Taiwan, and Denmark [7, 8, 22].

There were more males than females receiving atypical antipsychotics in this study, similar to previous findings that also revealed sex differences with male predominance [6, 23, 24]. The fact that schizophrenia, like other mental disorders, is involved in complex biological (hormonal) and psychosocial interactions seems to cause sex differences. For many years, several studies have reported sex differences in the age at onset for schizophrenia [25]. Males have an earlier age at onset for schizophrenia (before 25 years) than females (after 25 years) [26]. An increasing number of studies are examining this topic and exploring the association between sex

differences and the aetiology of psychosis disorders. Oestrogen seems to be psychoprotective and to influence the development and functioning of the brain in females, whereas hypothalamic–pituitary–gonadal dysfunction can influence both sexes [27]. On the other hand, some recent studies argue that the usual male predominance found in schizophrenia has become less apparent or that there is no sex difference [4, 7, 8]. Evidence regarding the sex difference in the risk of schizophrenia is still inconclusive [23].

While there is a significant increase in the use of atypical antipsychotics in children and adolescents worldwide, there are important gaps involving effectiveness, safety and effects in long-term use [11, 28]. Approximately 36% of patients aged 12 or below were using some of these atypical antipsychotics (risperidone, clozapine, olanzapine, quetiapine or ziprasidone), and none of these medications are approved for use in this age range (under 13 years) for the treatment of schizophrenia according to the National Sanitary Surveillance Agency (ANVISA-Brazil), Food and Drug Administration (FDA-US), or Medicines & Healthcare products regulatory Agency (MHRA-UK) [15, 16, 29].

Olanzapine, risperidone and quetiapine are approved for the treatment of schizophrenia only from 13 years old according to the ANVISA and FDA, while clozapine and ziprasidone are not approved for use among children and adolescents [16, 29]. However, the use of these drugs is increasing worldwide and exposes patients to potentially unnecessary harm.

Two systematic reviews assessed the effects of the use of antipsychotics in children (n=6 RCTs, 256 participants before 13 years) [11] and adolescents (n=13 RCTs, 1112 patients 13-18 years) [28] diagnosed with schizophrenia and identified benefits in using antipsychotics, but neither could conclude that any one antipsychotic is better than another, except clozapine. Clozapine is a good option for children and adolescents with treatment-resistant schizophrenia [9, 11, 14]. However, children and adolescents were more likely to show adverse effects; for instance, olanzapine, risperidone, and clozapine were often associated with weight gain in adolescents [12, 28]. Children who received clozapine showed a higher rate of neutropenia [11].

The high prescription rate of risperidone followed by olanzapine for the treatment of children and adolescents with schizophrenia has been confirmed in other studies [7, 17, 30]. This can be attributed to the increase in the diagnosis of schizophrenia and other mental disorders in this age group, the implementation of

diagnostic criteria for schizophrenia, improved access to intervention services and an increase in treatment capacity [4, 8].

In addition, the diagnosis is complex, and the psychotic experience may be misdiagnosed as early-onset schizophrenia or be the manifestations of other mental disorders, such as behavioural disorders, anxiety disorders, affective disorders and developmental disorders [1, 14]. The use of off-label atypical antipsychotics to treat these disorders is also a common practice and can inflate the consumption of these medicines [17, 30, 31]. To verify this hypothesis, further and extensive research should be conducted.

This scenario in the real world is a concern, given the expansion in the profile of users of antipsychotics and the diagnoses for which they are used. The majority of antipsychotic use is off-label, and the effects on the developing brain of early and prolonged exposure to atypical antipsychotics are unknown [31, 32].

For instance, among antipsychotics, risperidone is often used for the treatment of disruptive behaviour disorders, including aggression and conduct disorders, attention-deficit-hyperactivity disorder (ADHD) and autism, despite little evidence regarding its effectiveness [33]. Evidence has shown that risperidone reduces aggression and conduct problems compared to placebo in patients aged 5 to 18 years old [33]. The effectiveness of risperidone in the treatment of ADHD is unclear [34], and autism shows some benefits in irritability, repetition and social withdrawal [35].

The prescribed doses are in compliance with the Brazilian clinical protocol, although there is no specific protocol for treatment in children and adolescents in the country [20]. The doses also corroborate the dosage recommended by British National Formulary for children, which recommends starting with low doses and gradually titrating upwards over the weeks [15].

Although no guidelines recommend sex as a factor in the choice of antipsychotic or dose, patient sex should be considered by clinicians. Data are conflicting, and clinical implications exist, suggesting that females have a better response to antipsychotic treatment and require lower doses than males [36-38]. We found a slight sex difference only in the dose of quetiapine and risperidone for males in the 13-17 year age group. Another study conducted in Taiwan found no sex difference in the prescribed doses of atypical antipsychotics [7]. The clinical response to antipsychotic treatment seems to vary between males and females, and more studies are needed.

Strengths and Limitations

To our knowledge, this is the first study to investigate sex differences in children and adolescents who received atypical antipsychotics with a diagnosis of schizophrenia in Brazil. The data were double checked, which increases the reliability of the findings. The database used represents the users of the public health system that covers more than 75% of the Brazilian population. There are few studies that report a large and representative population of children and adolescents who received antipsychotics in real words.

There are some limitations. The database is reliable and representative for studies of drug use, but they record only supply of the drugs, not whether the drugs were taken. Data outside SUS via were not captured in our analysis. We were unable to explore the concurrent use of other psychotropic drugs and adverse reactions, because the database used was not created to answer the specific research questions, it was health administrative data.

Conclusion

Despite limited evidence regarding the safety and efficacy of atypical antipsychotics in children and adolescents, this study revealed significant use of these drugs in this age group, and a large majority of these were boys. The findings support the sex difference, especially in the 13-17 year age group and in the choice of antipsychotic use, with greater emphasis on the use of risperidone and olanzapine.

The implementation of clinical protocols for the treatment of children and adolescents is needed and should be a key priority of mental health services in Brazil, since some antipsychotic prescriptions are off-label and the long-term effects are still known. The findings could also contribute to improving the use of atypical antipsychotics and the pharmacotherapy management of children and adolescents with schizophrenia in the real world. Furthermore, it suggests that sex differences should be considered in future research and clinical practice.

DECLARATIONS:

Funding: this study was sponsored by The São Paulo Research Foundation (Fapesp), grant numbers 2017/20668-7

Competing interests: The authors declare that they have no competing interests

Availability of data and material: The data generated and analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Izabela Fulone, Marcus T. Silva and Luciane C. Lopes. The draft of the manuscript was written by Izabela Fulone and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics approval: The study used only secondary data from unrestricted access, obtained from the national administrative database, therefore it is exempt from the need for submission to Ethics Council as a sole paragraph of Resolution of the National Health Council No. 510/2016.

Consent for publication: not applicable

REFERENCES

1. Driver DI, Thomas S, Gogtay N, Rapoport JL. Childhood-Onset Schizophrenia and Early-onset Schizophrenia Spectrum Disorders: An Update. Child and adolescent psychiatric clinics of North America. 2020; 29(1):71-90.

2. Preda AB, Bora RG. Esquizofrenia. BMJ Best Practice. 2019. https://bestpractice-bmj.com.libaccesslibmcmasterca/topics/en-gb/406/pdf/406pdf. Accessed 12 Nov 2019.

3. Gilberg C. Schizophrenia in children and adolescents. In: Remischmidt H, editor. Epidemiology of early onset schizophrenia. Cambridge: Cambridge University Press; 2001. p 43-59.

4. Okkels N, Vernal DL, Jensen SO, McGrath JJ, Nielsen RE. Changes in the diagnosed incidence of early onset schizophrenia over four decades. Acta psychiatrica Scandinavica 2013; 127(1):62-68.

5. Thomsen PH. Schizophrenia with childhood and adolescent onset: a nationwide register-based study. Acta psychiatrica Scandinavica. 1996; 94(3):187-193.

6. Takahashi S, Matsuura M, Tanabe E, Yara K, Nonaka K, Fukura Y, Kikuchi M, Kojima T. Age at onset of schizophrenia: gender differences and influence of temporal socioeconomic change. Psychiatry and clinical neurosciences. 2000; 54(2):153-156.

7. Hsu CW, Lee SY, Wang LJ. Gender differences in the prevalence, comorbidities and antipsychotic prescription of early-onset schizophrenia: a nationwide population-based study in Taiwan. European child & adolescent psychiatry. 2019; 28(6):759-767.

8. Kühl JOG, Laursen TM, Thorup A, Nordentoft M. The incidence of schizophrenia and schizophrenia spectrum disorders in Denmark in the period 2000-2012. A register-based study. Schizophrenia research. 2016; 176(2-3):533-539.

9. National Institute for Health and Care Excellence. Psychosis and schizophrenia in children and young people. 2015. https://www.ncbi.nlm.nih.gov/books/NBK552055/. Accessed 03 Nov 2020.

10. Vyas NS, Gogtay N. Treatment of early onset schizophrenia: recent trends, challenges and future considerations. Frontiers in psychiatry. 2012; 3:29.

11. Kennedy E, Kumar A, Datta SS. Antipsychotic medication for childhood-onset schizophrenia. The Cochrane database of systematic reviews. 2007; 3:Cd004027.

12. Harvey RC, James AC, Shields GE. A Systematic Review and Network Meta-Analysis to Assess the Relative Efficacy of Antipsychotics for the Treatment of Positive and Negative Symptoms in Early-Onset Schizophrenia. CNS drugs. 2016; 30(1):27-39.

13. Alves MR, Bergamaschi CC, Sorrilha FB, Fulone I, Barberato-Filho S, Mayer RCF, Melo DO, Lopes L. Critical appraisal and comparison of recommendations of clinical practice guidelines for treatment of schizophrenia in children and adolescents: a methodological survey protocol. BMJ open. 2020; 10(9):e038646.

14. Abidi S, Mian I, Garcia-Ortega I, Lecomte T, Raedler T, Jackson K, Jackson K, Pringsheim T, Addington D. Canadian Guidelines for the Pharmacological Treatment of Schizophrenia Spectrum and Other Psychotic Disorders in Children and Youth. Canadian journal of psychiatry. 2017; 62(9):635-647.

15. British National Formulay (BNF) for children 2019-2020. 2019. bnfc.nice.org.uk. Acessed 03 Nov 2020.

16. Klasco R. DRUGDEX System [Internet].Greenwood Village (Colorado): Thomson Micromedex; [1974-2019]. https://wwwmicromedexsolutions-com. Acessed 03 Nov 2020.

17. Curtis LH, Masselink LE, Østbye T, Hutchison S, Dans PE, Wright A, Krishnan RR, Schulman KA. Prevalence of atypical antipsychotic drug use among commercially insured youths in the United States. Archives of pediatrics & adolescent medicine. 2005; 159(4):362-366.

18. Bachmann CJ LT, Glaeske G, Hoffmann F. Antipsychotic prescription in children and adolescents: an analysis of data from a German statutory health insurance company from 2005 to 2012. Dtsch Arztebl Int. 2014; 111(3):25-34.

19. BRAZIL. Indicadores básicos para a saúde no Brasil: conceitos e aplicações / Rede Interagencial de Informação para a Saúde - Ripsa. 2 ed. Brasília:

Organização Pan-Americana da Saúde, 2008. 349 p. http://tabnet.datasus.gov.br/tabdata/livroidb/2ed/indicadores.pdf. Accessed 12 Nov 2019.

20. BRAZIL. Protocolo clínico e diretrizes terapêuticas. Esquizofrenia. 2013. http://portalarquivos.saude.gov.br/images/pdf/2014/abril/02/pcdt-esquizofrenia-livro-2013.pdf. Accessed 12 Nov 2019.

21. World Health Organization. WHO Collaboration Centre for Drug Statistics Methodology. ATC/DDD Index 2020. atc_ddd_index. Accessed 10 Nov 2020.

22. Chen W, Cepoiu-Martin M, Stang A, Duncan D, Symonds C, Cooke L, Pringsheim T. Antipsychotic Prescribing and Safety Monitoring Practices in Children and Youth: A Population-Based Study in Alberta, Canada. Clinical drug investigation. 2018; 38(5):449-455.

23. Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. Archives of general psychiatry. 2003; 60(6):565-571.

24. Jerrell JM, McIntyre RS. Factors Differentiating Childhood-Onset and Adolescent-Onset Schizophrenia: A Claims Database Study. Prim Care Companion CNS Disord. 2016; 2(18).

25. Angermeyer MC, Kühn L. Gender differences in age at onset of schizophrenia. An overview. European archives of psychiatry and neurological sciences. 1988; 237(6):351-364.

26. Li R, Ma X, Wang G, Yang J, Wang C. Why sex differences in schizophrenia? J Transl Neurosci (Beijing). 2016; 1(1):37-42.

27. Riecher-Rössler A, Butler S, Kulkarni J: Sex and gender differences in schizophrenic psychoses-a critical review. Archives of women's mental health. 2018; 21(6):627-648.

28. Kumar A, Datta SS, Wright SD, Furtado VA, Russell PS: Atypical antipsychotics for psychosis in adolescents. The Cochrane database of systematic reviews. 2013; 10:Cd009582.

29. BRAZIL. National Sanitary Surveillance Agency (ANVISA). Bulário eletrônico. http://www.anvisa.gov.br/datavisa/fila_bula/index.asp. Accessed 20 Nov 2020.

30. Schröder C, Dörks M, Kollhorst B, Blenk T, Dittmann RW, Garbe E, Riedel O. Outpatient antipsychotic drug use in children and adolescents in Germany between 2004 and 2011. European child & adolescent psychiatry. 2017; 26(4):413-420.

31. Dinnissen M, Dietrich A, van der Molen JH, Verhallen AM, Buiteveld Y, Jongejan S, Troost PW, Buitelaar JK, Hoekstra PJ, Van den Hoofdakker BJ.

Prescribing antipsychotics in child and adolescent psychiatry: guideline adherence. European child & adolescent psychiatry. 2020; 29(12):1717-1727.

32. Vitiello B. Pediatric psychopharmacology and the interaction between drugs and the developing brain. Canadian journal of psychiatry. 1998; 43(6):582-584.

33. Loy JH, Merry SN, Hetrick SE, Stasiak K. Atypical antipsychotics for disruptive behaviour disorders in children and youths. The Cochrane database of systematic reviews. 2012; 9:Cd008559.

34. Thomson A, Maltezos S, Paliokosta E, Xenitidis K. Risperidone for attention-deficit hyperactivity disorder in people with intellectual disabilities. The Cochrane database of systematic reviews. 2009; 2:Cd007011.

35. Jesner OS, Aref-Adib M, Coren E. Risperidone for autism spectrum disorder. The Cochrane database of systematic reviews. 2007;1:Cd005040.

36. Aichhorn W, Marksteiner J, Walch T, Zernig G, Hinterhuber H, Stuppaeck C, Kemmler G. Age and gender effects on olanzapine and risperidone plasma concentrations in children and adolescents. Journal of child and adolescent psychopharmacology. 2007 17(5):665-674.

37. Usall J, Suarez D, Haro JM. Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. Psychiatry research. 2007; 153(3):225-231.

38. Eugene AR, Masiak J. A pharmacodynamic modelling and simulation study identifying gender differences of daily olanzapine dose and dopamine D2-receptor occupancy. Nordic journal of psychiatry. 2017; 71(6):417-424.

5.2.3 Artigo científico 5 – Perfil de utilização de antipsicóticos de segunda geração em pacientes com esquizofrenia atendidos no Sistema Único de Saúde

O artigo científico *"*Perfil de utilização de antipsicóticos de segunda geração em pacientes com esquizofrenia atendidos no Sistema Único de Saúde*"* teve como objetivo caracterizar o perfil de utilização de antipsicóticos de segunda geração em pacientes com esquizofrenia ou transtorno esquizoafetivo atendidos no Sistema Único de Saúde com ênfase nas características demográficas, clínicas, medidas de exposição, adesão e abandono ao reabastecimento de antipsicóticos.

A formatação seguiu as regras da revista Ciência & Saúde Coletiva e foi enviado em 07/12/2020. Encontra-se em fase de revisão.

Revista: Ciência & Saúde Coletiva
ISSN: ISSN 1413-8123
Versão online: 1678-4561
Fator de impacto: 1,008
Classificação Webqualis/Capes, área de Farmácia, 2020: A3

Perfil de utilização de antipsicóticos de segunda geração em pacientes com esquizofrenia atendidos no Sistema Único de Saúde

Izabela Fulone[1]; Marcus Tolentino Silva[1]; Luciane Cruz Lopes[1*]

[1]Programa de Pós- graduação em Ciências Farmacêuticas, Universidade de Sorocaba, Sorocaba, Estado de são Paulo, Brasil

***Luciane Cruz Lopes (autor correspondente)**
Pós- graduação em Ciências Farmacêuticas, Universidade de Sorocaba, Sorocaba, Estado de são Paulo, Brasil
Rodovia Raposo Tavares, KM 92,5 - Sorocaba, Estado de São Paulo, Brasil
CEP: 18023-000
Telefone: 55 19 99781-8441 Fax: 55 15 2101-7074

E-mail: luslopesbr@gmail.com; luciane.lopes@prof.uniso.br;

Conflito de interesse: não
Financiamento: Fapesp, processo n° 2017/20668-7
Número de caracteres com espaço: 17.532
Número de referências: 36
Número de figuras: 1
Número de tabelas: 4
Material suplementar: 1

RESUMO

Objetivo: Caracterizar o perfil de utilização de antipsicóticos de segunda geração (SGA) em pacientes com esquizofrenia ou transtorno esquizoafetivo atendidos no Sistema Único de Saúde (SUS).

Método: estudo transversal descritivo desenvolvido a partir dos registros das Autorizações de Procedimentos de Alta Complexidade contidos no Sistema de Informações Ambulatoriais do SUS (SIA/SUS), referente ao período de 2008 a 2017.

Resultados: dos 759.654 pacientes identificados, 50,5% eram mulheres, idade de 44 anos (±0,02), residentes da região sudeste (60,2%) e com diagnóstico de esquizofrenia paranoide (77,6%). Destes, 8,6% eram crianças/adolescentes (até 18 anos), 65,6% adultos (19 a 59 anos) e 21,2% idosos (≥ 60 anos). Houve prevalência do gênero masculino entre as crianças/adolescentes e adultos. Nas crianças/adolescentes, destacou-se o uso de risperidona (63,3%); nos adultos, a olanzapina (34,0%) e; nos idosos a quetiapina (47,4%). A troca do uso de SGA foi realizada com maior frequência nos adultos (14,5%). O tempo médio de utilização do SGA foi de 32 meses (±0,4), o abandono ao programa em seis meses foi 24,8% e; 8,2% retiraram o medicamento uma única vez.

Conclusão: o padrão de uso dos SGA diferiu segundo a faixa etária. Os achados poderão direcionar políticas públicas bem como o planejamento de ações, a oferta desses medicamentos de alto valor unitário e a melhoria do tratamento da esquizofrenia no âmbito do SUS.

Palavras-chaves: uso de medicamentos; antipsicóticos, Sistema Único de saúde; esquizofrenia;

ABSTRACT

Objective: To characterize the use profile of second-generation antipsychotics (SGA) in patients with schizophrenia or schizoaffective disorder seen in the Brazilian National Health System (SUS).

Method: a descriptive cross-sectional study developed from the records of the Authorities for High Complexity Procedures of the SUS Outpatient Information System (SIA/SUS), referring to the period from 2008 to 2017.

Results: of the 759,654 identified patients, 50.5% were women, aged 44 years (± 0.02), from the southeastern region (60.2%) and diagnosed with paranoid schizophrenia (77.6%), 8 6% children / adolescents (up to 18 years old), 65.6% adults (19 to 59 years old) and 21.2% elderly (≥ 60 years old). There was a prevalence of males among children / adolescents and adults. In children / adolescents, the use of risperidone stood out (63.3%); in adults, olanzapine (34.0%) and; in the elderly, quetiapine (47.4%). The switch of SGA occurred more frequently in adults (14.5%). The average time of use of the SGA was 32 months (± 0.4), the abandonment to the program in six months was 24.8% and; 8.2% withdrew the medication only once.

Conclusion: the pattern of use of SGA differed according to age and gender. The findings may guide public policies as well as the planning of actions, the offer of these drugs with high unit value and the improvement of the treatment of schizophrenia within the scope of SUS.

Keywords: drug utilization; antipsychotics, Unified Health System; schizophrenia;

INTRODUÇÃO

A esquizofrenia é um transtorno mental grave, crônico, debilitante, que atinge cerca de 0,7% da população mundial (1). No Brasil, a prevalência de psicoses em geral é de 0,3-2,4% e de esquizofrenia próxima a 1% da população (2, 3).

O início dos sintomas da esquizofrenia ocorre em adultos jovens, geralmente antes dos 25 anos nos homens e antes dos 35 anos nas mulheres (1). O aparecimento da esquizofrenia de início precoce (antes dos 18 anos) e de início tardio (nos mais velhos) não são muito frequentes, o diagnóstico é mais complexo e as evidências sobre efetividade de segurança do tratamento são limitadas (4, 5)

Os antipsicóticos representam o pilar para o tratamento da esquizofrenia e outros transtornos psicóticos (6). Desde que foram introduzidos no mercado nos anos noventa, os antipsicóticos de segunda geração (SGA) tem revolucionado o tratamento da esquizofrenia, especialmente em casos de refratariedade. Estudos mostram que não há diferenças de efetividade entre os SGA, exceto a clozapina (7). As diferenças residem no perfil de efeitos adversos, cuja principal vantagem dos SGA em relação aos antipsicóticos de primeira geração é a maior tolerabilidade e menor risco de efeitos extrapiramidais (8). No entanto, esses fármacos apresentam maior risco de síndromes metabólicas e maior custo (9).

O Sistema Único de Saúde (SUS) fornece antipsicóticos de primeira geração (clorpromazina e haloperidol) e SGA (clozapina, olanzapina, quetiapina, risperidona e ziprasidona) para tratamento da esquizofrenia e transtorno esquizoafetivo. Os SGA são considerados de alto custo, pertencem ao Componente Especializado da Assistência Farmacêutica e são dispensados somente após análise da solicitação e cumprimento dos requisitos apresentados no protocolo clínico brasileiro específico (10).

Nos últimos anos, houve um aumento exponencial no uso de SGA em várias partes do mundo, na população em geral e nos grupos mais vulneráveis como crianças e idosos (11-14). As principais preocupações incluem o amplo uso *off-label* e a exposição dos grupos mais vulneráveis aos potenciais efeitos adversos.

Os custos com os SGA corresponderam à maior parte dos gastos relacionados ao tratamento da esquizofrenia pelo SUS (15, 16). No período de 2000 a 2010, a olanzapina foi responsável por cerca de 63% do total de gastos com SGA e os

usuários de clozapina tiveram a maior média de gasto com acompanhamento psiquiátrico ambulatorial e hospitalização psiquiátrica (16).

Considerando o alto consumo de SGA em várias partes do mundo, a exposição aos riscos associados à sua utilização e o alto custo que isso representa, particularmente ao sistema de saúde brasileiro, torna-se oportuno conhecer o perfil de utilização destes medicamentos no cenário nacional de vida real. O objetivo deste trabalho foi caracterizar o perfil de utilização de SGA em pacientes com esquizofrenia ou transtorno esquizoafetivo atendidos no SUS.

Método

Desenho do estudo

Estudo transversal descritivo.

Cenário

Utilizou-se como fonte de informação os registros relacionados à Autorização de Procedimentos de Alta Complexidade (APAC) armazenados no Sistema de Informação Ambulatorial do SUS (SIA/SUS). Os dados individualizados estão publicamente disponíveis no Departamento de Informática do SUS a partir de 2008.

Esse banco de dados administrativo disponibiliza informações sobre o fornecimento de medicamentos pertencentes ao Componente Especializado da Assistência Farmacêutica (CEAF), antigamente chamados de medicamentos de alto custo, em nível ambulatorial, para o tratamento de determinadas doenças de acordo com os Protocolos Clínicos e Diretrizes Terapêuticas (PCDT) (17).

O acesso a esses medicamentos ocorre por meio do preenchimento de um laudo de solicitação de medicamentos (LME) pelo médico prescritor. Em seguida, o LME é analisado e verificado se cumpre com os requisitos presente no PCDT. Se deferido, o LME é autorizado e origina-se uma APAC, neste caso relacionada ao fornecimento dos medicamentos, com cadastramento do usuário no banco de dados nacional para fins gerenciais e de cobrança.

O CEAF fornece os seguintes SGA para tratamento da esquizofrenia e do transtorno esquizoafetivo: clozapina, olanzapina, risperidona, quetiapina e ziprasidona (10, 18).

Participantes

Foram incluídos todos os pacientes com diagnóstico de esquizofrenia e transtorno esquizoafetivo admitidos pelo menos uma vez no programa de acesso aos medicamentos pertencentes ao CEAF no período de 1 de janeiro de 2008 a 31 de dezembro de 2017.

Variáveis

Foram consideradas as seguintes categorias de variáveis:

- **Características demográficas:** sexo, idade, etnia, região de residência e ano de entrada no programa (definido pela data em que o indivíduo recebeu o primeiro SGA no programa);

- **Características clínicas:** diagnóstico principal segundo CID-10; média de tempo de tratamento (número de meses com registro de procedimentos na APAC), SGA utilizado na entrada do programa e proporção de pacientes que trocaram pelo menos uma vez o SGA.

- **Medidas de exposição**: número de receitas dispensadas (número de vezes que o paciente procura o serviço de saúde do SUS para dispensação do SGA), tempo em posse do medicamento (dias coberto pela prescrição ou número de dias que o paciente tem o medicamento acessível), dose média diária e proporção de dose média diária/Dose Diária Definida (DDD). A DDD é uma unidade de medida padrão utilizada em estudos de utilização de medicamentos, preconizada pela Organização Mundial da Saúde (OMS), que nos permite comparar o uso de medicamentos de diferentes países e populações. É definida pela dose média de manutenção diária de um medicamento usado para sua principal indicação em adultos (19). A DDD dos SGA aqui estudados são: clozapina (300,0 mg), olanzapina (10,0 mg), risperidona (5,0 mg), quetiapina (400,0 mg) e ziprasidona (80,0 mg) (19).

- Medidas de adesão ao reabastecimento de SGA de cada paciente: número total de dias cobertos pela prescrição durante o estudo (ou data final de apresentação da última APAC subtraído pela data inicial da primeira APAC) dividido pelo tempo estudado (data do período final do estudo, dezembro de 2017, subtraído da data inicial

da primeira APAC) e multiplicado por 100. Essa proporção de tempo foi categorizada em ≥80% aderente, 50-80% parcialmente aderente, <50% não aderente.

$$\text{Adesão ao reabastecimento} = \frac{\textit{tempo total observado durante o estudo x 100}}{\textit{tempo estudado}}$$

-Medidas de abandono ao reabastecimento: proporção de pacientes que a data do último reabastecimento ocorre antes de completar 6 meses de acompanhamento ou que apresentam apenas uma entrada na base da Apac.

As medidas de exposição, adesão e abandono ao reabastecimento foi adaptada à metodologia desenvolvida por Rodrigues (20).

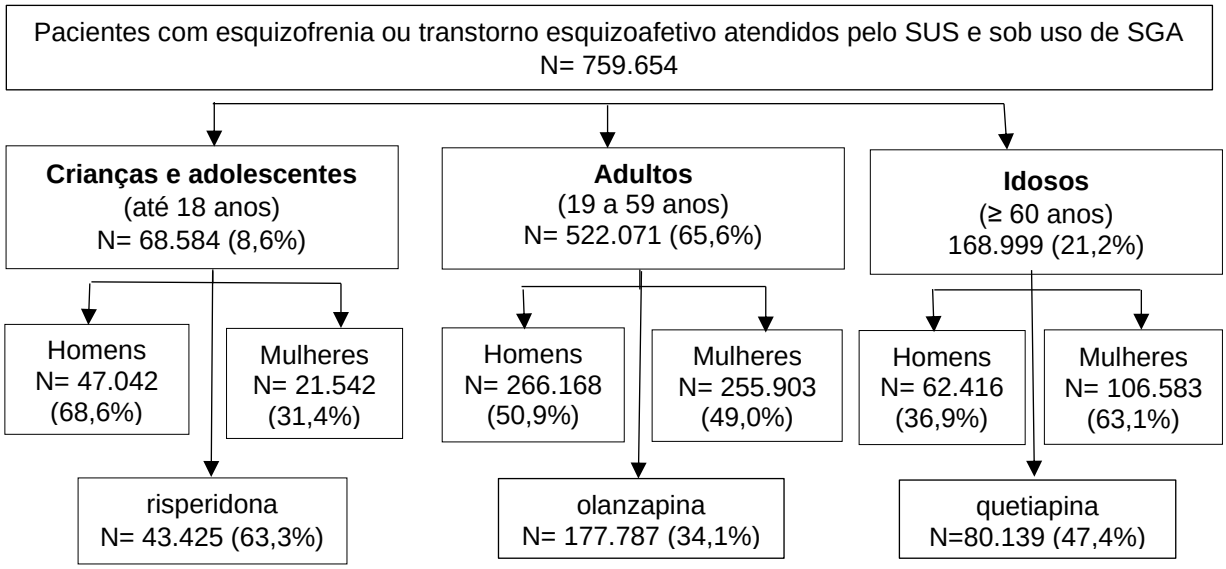
Análise dos dados

As variáveis contínuas foram expressas por média e desvio padrão, e as variáveis categóricas como porcentagem para estatística descritiva.

Resultados

Foram identificados 759.654 pacientes com diagnóstico de esquizofrenia ou transtorno esquizoafetivo com pelo menos uma entrada no banco de dados SIA/SUS. Cerca de 68.584 (8,6%) eram crianças/adolescentes (até 18 anos), 522.071 (65,6%) adultos (19-59 anos) e 168.999 (21,2%) eram idosos (≥ 60 anos), Figura 1.

Figura 1 – Fluxograma da caracterização do uso de antipsicóticos de segunda geração



No geral, 50,5% eram mulheres, adultas, com média de idade de 44 anos (± 0,1), residentes na região sudeste. O perfil dos usuários diferiu de acordo com a faixa etária. A maioria das crianças/adolescentes (68,6%) e adultos (50,9%) eram homens, enquanto que a maioria dos idosos eram mulheres (63,1%), Tabela 1.

Tabela 1 - Características demográficas dos participantes do estudo.

Variáveis	Crianças e adolescentes* N= 68.584	Adultos& N= 522.071	Idosos# N= 168.999	Total N= 759.654
Sexo				
Mulheres	21.542 (31,4)	255.903 (49,0)	106.583 (63,1)	384. 028 (50,5)
Homens	47.042 (68,6)	266.168 (50,9)	62.416 (36,9)	375.626 (49,5)
Idade (em anos), média (DP)				
	12,78 (0,1)	38,45 (0,1)	74,24 (0,1)	44.096 (0,1)
Etnia				
Branca	8.241 (12,0)	55.274 (10,6)	24.641 (14,6)	88.156 (11,1)
Preta	773 (1,1)	5.809 (1,1)	1.430 (0,8)	8. 012 (1,0)
Parda	5.620 (8,2)	34.782 (6,6)	8.612(5,1)	49. 014 (6,2)
Amarela	1.536 (2,2)	12.045 (2,3)	2.783 (1,6)	16. 364 (2,1)
Indígena	33 (0,1)	93 (0,02)	20 (0,01)	146 (0,02)
Sem informação	52.381 (76,4)	414.068 (79,3)	131.513 (77,8)	633.962 (79,7)
Região de residência				
Norte	1.855 (2,7)	14.313 (2,7)	2.067 (1,2)	18.235 (2,4)
Nordeste	14.312 (20,9)	104.933 (20,1)	23.416 (13,9)	142. 661 (18,8)
Sudeste	39.681 (57,9)	296.424 (56,8)	121.524 (71,9)	457. 629 (60,2)
Sul	8.829(12,9)	66.253 (12,7)	13.133 (7,8)	88. 215 (11,6)
Centro-oeste	3.907 (5,7)	40.148 (7,7)	8.859 (5,2)	52. 914 (6,9)
Ano de entrada no programa				
2008	12.168 (17,7)	118.427 (22,7)	24.640 (14,6)	155. 235 (20,4)
2009	6.116 (8,9)	46.750 (8,9)	13.191 (7,8)	66.057 (8,7)
2010	6.321 (9,2)	43.510 (8,3)	16.141 (9,5)	65.972 (8,7)
2011	6.545 (9,5)	44.545 (8,5)	15.087 (8,9)	66. 177 (8,7)
2012	5.798 (8,5)	37.571 (7,2)	12.960 (7,7)	56. 329 (7,4)
2013	5.864 (8,5)	41.059 (7,9)	14.600 (8,6)	61. 523 (8,1)
2014	6.169 (8,9)	41.162 (7,9)	16.056 (9,5)	63.387 (8,3)
2015	6.991 (10,2)	53.317 (10,2)	19.589 (11,6)	79.897 (10,5)
2016	6.717 (9,8)	53.678 (10,3)	19.499 (11,5)	79. 894 (10,5)
2017	5.895 (8,6)	42.052 (8,1)	17.236 (10,2)	65.183 (8,6)

*crianças/adolescentes: até 18 anos; adultos: 19-59 anos; idosos: ≥60 anos

Independente da faixa etária, o diagnóstico mais frequente foi a esquizofrenia paranoide-F20.0 (77,6%), seguida de outras esquizofrenias-F20.8 (11,0%). O tempo médio de tratamento foi de 32 meses (±0,4), variando entre 24,7 (±0,1) meses para os idosos, 28,8 (±0,1) meses para crianças/adolescentes e 34,9 (±0,1) meses para os adultos.

Ao longo dos dez anos, o SGA mais prescrito foi a risperidona (33,1%), seguida da olanzapina (29,6%), quetiapina (27,7%), ziprasidona (5,1%) e clozapina (4,5%). Se considerar apenas crianças/adolescentes, a risperidona se destaca com 63,3%. A olanzapina foi o antipsicótico mais prescrito aos adultos (34,1%), seguido da risperidona (30,3%). Já nos idosos houve predomínio do uso de quetiapina (47,4%), seguida de risperidona (29,3%).

Se considerar a proporção de uso de SGA por ano, a risperidona foi a mais prescrita às crianças nos dez anos de estudo. Nos idosos, a maior proporção de uso de quetiapina ocorreu a partir de 2010. E nos adultos, nos anos de 2010 a 2012, houve maior uso de risperidona, e nos demais, olanzapina (Tabela S1 a S4 - Material Suplementar).

Aproximadamente 9% das crianças/adolescentes, 14% dos adultos e 8% dos idosos fizeram pelo menos uma troca de SGA ao longo do tratamento.

Tabela 2 – Características clínicas dos participantes do estudo.

Variáveis	Crianças e adolescentes* N= 68.584	Adultos[&] N= 522.071	Idosos[#] N= 168.999	Total N= 759.654
Diagnóstico principal (CID-10)				
Esquizofrenia paranoide (F20.0)	49.847(72,7)	413.848 (79,3)	126.023 (74,6)	589.718 (77,6)
Esquizofrenia hebefrênica (F20.1)	3.462 (5,1)	15.081 (2,9)	3.372 (2,0)	21.915 (2,9)
Esquizofrenia catatônica (F20.2)	306 (0,5)	2.346 (0,5)	674 (0,4)	3.326 (0,4)
Esquizofrenia indiferenciada (F20.3)	2.021 (2,9)	12.961 (2,5)	4.093 (2,4)	19.075 (2,5)
Depressão pós-esquizofrênica (F20.4)	203 (0,3)	2.667 (0,5)	1.198 (0,7)	4.068 (0,5)
Esquizofrenia residual (F20.5)	858 (1,3)	16.071 (3,1)	5.794 (3,4)	22.723 (2,9)
Esquizofrenia simples (F20.6)	944 (1,4)	5.304 (1,1)	2.021 (1,2)	8,269 (1,1)
Outras esquizofrenias (F20.8)	10,499 (15,3)	48.758 (9,4)	24.273 (14,4)	83.530 (11,0)
Transtorno esquizoafetivo do tipo maníaco (F25.0)	202 (0,3)	1.788 (0,4)	629 (0,4)	2.619 (0,3)
Transtorno esquizoafetivo do tipo depressivo (F25.1)	82 (0,1)	1.764 (0,4)	500 (0,3)	2.346 (0,3)
Transtorno esquizoafetivo do tipo misto (F25.2)	160 (0,2)	1.483 (0,3)	422 (0,3)	2.065 (0,3)

Tabela 2 (continuação) – Características clínicas dos participantes do estudo.

Variáveis	Crianças e adolescentes* N= 68.584	Adultos[&] N= 522.071	Idosos[#] N= 168.999	Total N= 759.654
Média de tempo de tratamento em meses (DP)				
	28,827 (±0,1)	34,905 (±0,1)	24,763 (±0,1)	32,100 (±0,4)
SGA¨ utilizado na entrada do programa				
clozapina	1.518 (2,2)	30.311 (5,8)	2.657 (1,6)	34.486 (4,5)
olanzapina	13.380 (19,5)	177.787 (34,1)	33.694 (19,9)	224.861 (29,6)
risperidona	43.425 (63,3)	158.415 (30,4)	49.512 (29,3)	251.352 (33,1)
quetiapina	8.106 (11,8)	122.167 (23,4)	80.139 (47,4)	210.412 (27,7)
ziprasidona	2.155 (3,2)	33.391 (6,4)	2.997 (1,8)	38.543 (5,1)
Pacientes que trocaram pelo menos uma vez o SGA¨				
	9.242 (13,5)	76.210 (14,6)	14.632 (8,6)	100.084 (13,2)

¨SGA: antipsicóticos de segunda geração; *crianças/adolescentes: até 18 anos; [&]adultos: 19-59 anos; [#]idosos: ≥60 anos; ¨SGA: antipsicóticos de segunda geração

A média de receitas de SGA dispensadas foi de 26,5 (±0,01) por paciente, variando de 1 até 120 receitas, que corresponde àquele paciente que permaneceu utilizando SGA ao longo dos dez anos do estudo (120 meses). A média de acompanhamento ou de posse do medicamento pelo programa foi de 963 dias (± 999,3) ou 32 meses.

Em geral, a média das doses prescritas segue as recomendações do PCDT. A proporção dose média/DDD foram menores para quetiapina (0,52) e risperidona (0,57), ou seja, menor do que 100% da DDD preconizada pela OMS, sugerindo o uso de doses mais baixas desses fármacos. Já a ziprasidona apresentou proporção dose média/DDD maior que 100%, sugerindo uso de doses mais altas e maior exposição, **Tabela 3.**

Tabela 3 - Medidas de exposição aos antipsicóticos.

Medidas de exposição	Total (N= 759.654)
Média de receitas dispensadas/paciente (DP)	26,5 (± 0,1)
Tempo em posse do medicamento em dias (DP)	963,1 (± 999,3)
Dose prescrita (DP)	
clozapina	
Dose média diária (mg/dia)	309,6 (± 192,3)
Dose média/DDD*	1,1 (± 0,6)
olanzapina	
Dose média diária (mg/dia)	10,2 (± 6,8)
Dose média/DDD*	1,1 (± 0,7)
risperidona	
Dose média diária (mg/dia)	2,9 (± 2,1)
Dose média/DDD*	0,6 (± 0,4)
quetiapina	
Dose média diária (mg/dia)	209,1 (± 207,8)
Dose média/DDD*	0,5 (± 0,5)

Tabela 3 (continuação) - Medidas de exposição aos antipsicóticos.

Medidas de exposição	Total (N= 759.654)
ziprasidona	
Dose média diária (mg/dia)	107,1 (± 75,2)
Dose média/DDD*	1,3 (±0,9)

*DDD preconizada pela Organização Mundial de Saúde: clozapina (300,0 mg), olanzapina (10,0 mg), risperidona (5,0 mg), quetiapina (400,0 mg), ziprasidona (80,0 mg)

Dos pacientes identificados neste estudo, 24,8% abandonaram o programa nos primeiros seis meses e 8,2% apresentaram uma única entrada no banco de dados, ou seja, retiraram o SGA uma única vez. A taxa de adesão ao reabastecimento de SGA foi alta, 81,9% dos pacientes eram aderentes ao programa e permaneceram no banco de dados por mais de 80% do período do estudo, Tabela 4.

Tabela 4 - Medidas de adesão e abandono ao reabastecimento de SGA.

Variáveis	N= 759.654 (100%)
Proporção de abandono ao reabastecimento de SGA	
Única entrada no banco de dados	62.550 (8,2)
Pacientes que saíram antes de 6 meses[&]	188.786 (24,8)
Proporção de adesão ao reabastecimento de SGA	
≥ 80%	622.191 (81,9)
50-80%	81.903 (10,8)
< 50%	55.561 (7,3)

DISCUSSÃO

Principais achados

Os achados deste estudo trazem potenciais informações sobre o padrão de utilização de SGA em pacientes com esquizofrenia ou transtorno esquizoafetivo atendidos pelo SUS em diferentes faixas etárias. O padrão de utilização diferiu segundo a faixa etária: a risperidona foi a mais prescrita para as crianças e adolescentes, a olanzapina para os adultos e a quetiapina para os idosos. A adesão ao reabastecimento de SGA durante o período do estudo foi alta e o abandono nos primeiros meses merece futuros estudos.

Comparação com outros estudos

O predomínio do sexo masculino em adultos e crianças/adolescentes endossam os achados de outras pesquisas e sugere mais uma vez que a

esquizofrenia acomete mais o sexo masculino e que seu aparecimento é mais precoce nos meninos. Já nos idosos, houve maior proporção de mulheres, coincidindo com outros achados (12) que preconizam que a esquizofrenia tardia acomete mais o sexo feminino, tem perfil sintomático um pouco diferente e melhor prognóstico (21, 22).

Nos dez anos deste estudo, a maioria dos pacientes identificados moravam na região sudeste quando entraram no programa, achado que pode sugerir uma relação de fatores socioeconômicos e o desencadear da esquizofrenia. A região sudeste do Brasil é a região com maior Índice de Desenvolvimento Humano (IDH: 0,79), maior renda domiciliar per capita e maior acesso aos serviços de saúde e aos medicamentos (23). Uma pesquisa nacional mostrou que o acesso aos serviços de saúde é fortemente influenciado pela região onde reside e pela condição social, com destaque a região sudeste (24). Paralelamente, outro estudo detectou que a esquizofrenia é mais prevalente na região sudeste (25).

Diferenças no perfil de utilização de SGA foram observadas de acordo com a faixa etária. Aproximadamente 9% dos usuários identificados tinham idade menor ou igual a 18 anos e a maioria dos SGA não são recomendados para essa faixa etária, pois a efetividade e segurança ainda não estão estabelecidas. De acordo com a Agência Nacional de Vigilância Sanitária (ANVISA) e a agência reguladora dos Estados Unidos *(Food and Drug Administration),* risperidona, olanzapina e quetiapina são aprovados para tratamento da esquizofrenia somente a partir dos 13 anos, e a clozapina e ziprasidona não são aprovadas para uso nesta população (até 18 anos) (26, 27).

As crianças são potencialmente mais susceptíveis aos efeitos adversos dos antipsicóticos e a escolha do antipsicótico deve ser feita de acordo com o perfil metabólico, cardiovascular e hormonal da criança (28). Ao longo dos dez anos, a risperidona foi o SGA mais utilizado pelas crianças e adolescentes, padrão este encontrado em outros estudos conduzidos nos Estados Unidos, Taiwan e Alemanha (11, 29, 30).

A olanzapina foi o SGA mais utilizados pelos adultos, seguido pela risperidona, quetiapina, ziprasidona e clozapina. A tendência de uso coincide com outra pesquisa realizada no Brasil nos anos de 2000 a 2010 (16). A olanzapina é um dos SGA mais caros e foi responsável pelo maior custo anual por paciente sob uso de SGA no Brasil (16). Comparado aos outros SGA, a olanzapina é a que causa mais ganho de peso e distúrbios metabólicos (31), e por sua vez, pode acarretar complicações à saúde dos

usuários, baixa adesão e até determinar sua troca por outro SGA que cause menos risco de ganho de peso (32).

A quetiapina foi o SGA mais utilizado pelos idosos, seguido da risperidona. Este fármaco apresenta menos distúrbios de movimento do que a risperidona, porém causa mais tontura, boca seca e sonolência (33). Os idosos apresentam benefícios com o uso de SGA e são bem tolerados desde que tenham baixo risco para efeitos extrapiramidais, distúrbios metabólicos e ganho de peso. Entretanto, as mudanças fisiológicas decorrente da idade avançada podem resultar em prolongamento do efeito dos antipsicóticos e maior susceptibilidade a efeitos adversos, portanto devem ser usados com cautela e em baixas doses (5, 34). Estudo tem mostrado associação entre o uso de antipsicóticos e aumento da mortalidade e do risco de acidente vascular cerebral e parada cardiorrespiratória em idosos (35, 36).

Apesar da sua superioridade em relação aos SGA, a clozapina foi o SGA menos prescrito em todas as faixas etárias. Isso pode ser explicado pelo fato de PCDT preconizar seu uso apenas após falha terapêutica de dois outros antipsicóticos (10).

As posologias identificadas seguem as recomendações do PCDT, conforme exigência para fornecimento de SGA. Os registros da APAC ao longo dos dez anos, mostraram que a maioria dos pacientes eram aderentes ao reabastecimento de antipsicóticos. Futuras análises serão conduzidas para avaliar a prevalência de *gaps* no reabastecimento e os fatores de risco à descontinuação ao tratamento.

Aproximadamente 33% dos usuários abandonaram o programa ou deixaram de realizar o reabastecimento de SGA antes de 6 meses, fato que pode impulsionar futuras pesquisas sobre as causas desse abandono e quais consequências isso acarreta ao sistema de saúde. Novas pesquisas são necessárias para avaliar a adesão e o abandono do paciente ao tratamento.

Força e Limitações

Este foi um dos poucos estudos que investigou o uso de SGA em pacientes com esquizofrenia ou transtorno esquizoafetivo atendidos no SUS, sem restrição de idade, ao longo de dez anos. Utilizou-se um importante e grande banco de dados do SUS (SIA/SUS), pouco explorado em pesquisas brasileiras, de difícil manejo, e que tem potencial para gerar valiosas informações para o SUS. Os dados foram duplamente checados, a fim de aumentar a confiabilidade.

Trata-se de um grande banco de dados administrativo, que não foi desenvolvido para fins de pesquisa, portanto, alguns dados clínicos não estavam presentes e poderiam estar sujeitos a erros de alimentação. Alguns campos não obrigatórios não estavam preenchidos, fato que impediu a realização de certas análises, como etnia, presença de comorbidades, diagnóstico secundário e mortalidade, etc. Além disso, não possui informações sobre as razões para a troca de SGA, para a não adesão ou para o abandono ao programa.

Os usuários avaliados no banco SIA/SUS são aqueles que recebem os SGA via SUS, portanto não capturamos informações sobre o padrão de uso dos SGA dos pacientes que adquiriram esses medicamentos em farmácias privadas. Foi utilizado o diagnóstico para esquizofrenia e transtorno esquizoafetivo informado no banco, não houve um processo de validação de diagnósticos, objetivo de outro estudo.

Conclusão

Os dados mostraram diferenças no perfil de utilização de SGA de acordo com a faixa etária do paciente. Parcela considerável de pacientes pertencentes aos extremos etários (crianças e idosos) estão expostos aos efeitos do SGA e merecem maior atenção. A elaboração de protocolos clínicos específicos para o tratamento da esquizofrenia em crianças/adolescentes, e em idosos poderiam auxiliar os profissionais na prática clínica, otimizar o tratamento e a qualidade dos cuidados prestados pelo SUS, especialmente aos indivíduos mais vulneráveis.

A utilização de grandes bases de dados administrativos, como os registros da APAC, permite gerar dados de interesse para a saúde pública. A tomada de decisão orientada por dados da vida real é uma tendência promissora e neste caso, os achados podem contribuir para o planejamento de ações, à oferta de SGA, o uso de recursos e a melhoria do tratamento e acompanhamento da esquizofrenia no âmbito do SUS.

REFERENCIAS

1. Preda A, Bota RG. Esquizofrenia. BMJ Best Practice (última atualização em 2019). [acessado em 19 nov. 2019]. Disponível em: bestpractice.bmj.com/topics/ptbr/406/pdf/406/Esquizofrenia.pdf

2. Andrade L, Walters EE, Gentil V, Laurenti R. Prevalence of ICD-10 mental disorders in a catchment area in the city of São Paulo, Brazil. Social psychiatry and psychiatric epidemiology 2002;37(7):316-25.

3. Almeida Filho N, Mari JJ, Coutinho E, França JF, Fernandes, JG, Andreoli SB, Busnello ED. Estudo multicêntrico de morbidade psiquiátrica em áres urbanas brasileiras (Brasília, Säo Paulo, Porto Alegre). Rev ABP-APAL. 1992;3(14):93-104.

4. National Collaborating Centre for Mental Health. National Institute for Health and Clinical Excellence: Guidance. Psychosis and Schizophrenia in Children and Young People: Recognition and Management. Leicester (UK): British Psychological Society and The Royal College of Psychiatrists, 2013.

5. Essali A, Ali G. Antipsychotic drug treatment for elderly people with late-onset schizophrenia. The Cochrane database of systematic reviews 2012(2):Cd004162.

6. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the Pharmacotherapy of Schizophrenia in Adults. Canadian journal of psychiatry Revue canadienne de psychiatrie 2017;62(9):604-16.

7. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. The British journal of psychiatry: the journal of mental science 2016;209(5):385-92.

8. National Collaborating Centre for Mental Health. National Institute for Health and Clinical Excellence Guidance. Psychosis and schizophrenia in adults: treatment and management. [acessado 2019 Set. 25]. Disponível em: nice.org.uk/guidance/cg178/evidence/full-guideline-490503565

9. Raben AT, Marshe VS, Chintoh A, Gorbovskaya I, Muller DJ, Hahn MK. The Complex Relationship between Antipsychotic-Induced Weight Gain and Therapeutic Benefits: A Systematic Review and Implications for Treatment. Frontiers in neuroscience 2017;11:741.

10. BRASIL. Ministério da Saúde. Secretaria de atenção à saúde. Protocolo Clínico e Diretrizes Terapêuticas. Esquizofrenia refratária. Brasília: Ministério da Saúde, 2013. 42p. 2013.

11. Curtis LH, Masselink LE, Østbye T, Hutchison S, Dans PE, Wright A, et al. Prevalence of atypical antipsychotic drug use among commercially insured youths in the United States. Archives of pediatrics & adolescent medicine 2005;159(4):362-6.

12. Kuo CL, Chien IC, Lin CH. Trends, correlates, and disease patterns of antipsychotic use among elderly persons in Taiwan. Asia-Pacific psychiatry: official journal of the Pacific Rim College of Psychiatrists 2016;8(4):278-86.

13. Roberts R, Neasham A, Lambrinudi C, Khan A. A quantitative analysis of antipsychotic prescribing trends for the treatment of schizophrenia in England and Wales. JRSM Open 2018;9(4):2054270418758570.

14. Lao KSJ, Tam AWY, Wong ICK, Besag FMC, Man KKC, Chui CSL, et al. Prescribing trends and indications of antipsychotic medication in Hong Kong from 2004 to 2014: General and vulnerable patient groups. Pharmacoepidemiology and drug safety 2017;26(11):1387-94.

15. Acurcio FA, Brandão CMR, Guerra Júnior AA, Cherchiglia ML, Andrade IG, Almeida AM, et al. Perfil demográfico e epidemiológico dos usuários de medicamentos de alto custo no Sistema Único de Saúde. J Revista Brasileira de Estudos de População 2009;26:263-82.

16. Barbosa WB, Costa JO, de Lemos LLP, Gomes RM, de Oliveira HN, Ruas CM, et al. Costs in the Treatment of Schizophrenia in Adults Receiving Atypical Antipsychotics: An 11-Year Cohort in Brazil. Applied health economics and health policy 2018;16(5):697-709.

17. BRASIL. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Assistência Famacêutica e Insumos Estratégicos. Da excepcionalidade às linhas de cuidado: o Componente Especializado da Assistência Farmacêutica. Brasília : Ministério da Saúde, 2010. 262 p.

18. BRASIL. Ministério da Saúde. Secretaria de atenção à saúde. Protocolo Clínico e Diretrizes Terapêuticas do Transtorno Esquizoafetivo. Brasília: Ministério da Saúde, 2014. 33p. 2014.

19. WHO. Organização Mundial da Saúde. ATC Index with DDD. [acessado 2020 Nov 27]. Disponível em: https://www.whocc.no/atc_ddd_index_and_guidelines/atc_ddd_index/.

20. CS R. Adesão e sobrevida de pacientes de um programa para doença de Alzheimer no Rio de Janeiro: um estudo baseado no relacionamento de dados [tese]. Rio de Janeiro (RJ): Universidade do Estado do Rio de Janeiro, 2013.

21. Harris MJ, Cullum CM, Jeste DV. Clinical presentation of late-onset schizophrenia. The Journal of clinical psychiatry. 1988;49(9):356-60.

22. Howard R, Rabins PV, Seeman MV, Jeste DV. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. The International Late-Onset Schizophrenia Group. The American journal of psychiatry 2000;157(2):172-8.

23. Brasil. Instituto Brasileiro de Geografia e Estatística. [acessado 2020 Nov 28]. Disponível em: https://www.ibge.gov.br/ 2020.

24. Travassos C, Oliveira EXGd, Viacava F. Desigualdades geográficas e sociais no acesso aos serviços de saúde no Brasil: 1998 e 2003. J Ciência & Saúde Coletiva. 2006;11:975-86.

25. Dornelas LTS, Dornelas, L. H. S., Dornelas, C. R. S., De Melo, G. F., Souza, N. B., Faria, T. A. V. Fatores socioeconomicos e esquizofrenia nas regioes brasileiras. Revista Científica Online 2019;11(1):8p.

26. KLASCO RK, editor. DRUGDEX System [Database on the Internet].Greenwood Village (Colorado): Thomson Micromedex; [1974-2019]. [acessado 09 Nov 2019]. Disponível em: https://www-micromedexsolutions-com

27. ANVISA. Agência Nacional de Vigilância Sanitária. Bulário eletrônico. o. [acessado 09 Nov 2020]. Disponível em: http://www.anvisa.gov.br/datavisa/fila_bula/index.asp.

28. Abidi S, Mian I, Garcia-Ortega I, Lecomte T, Raedler T, Jackson K, et al. Canadian Guidelines for the Pharmacological Treatment of Schizophrenia Spectrum and Other Psychotic Disorders in Children and Youth. Canadian journal of psychiatry Revue canadienne de psychiatrie. 2017;62(9):635-47.

29. Hsu CW, Lee SY, Wang LJ. Gender differences in the prevalence, comorbidities and antipsychotic prescription of early-onset schizophrenia: a nationwide population-based study in Taiwan. European child & adolescent psychiatry 2019;28(6):759-67.

30. Schröder C, Dörks M, Kollhorst B, Blenk T, Dittmann RW, Garbe E, et al. Outpatient antipsychotic drug use in children and adolescents in Germany between 2004 and 2011. European child & adolescent psychiatry 2017;26(4):413-20.

31. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, et al. Olanzapine versus other atypical antipsychotics for schizophrenia. The Cochrane database of systematic reviews 2010(3):Cd006654.

32. Mukundan A, Faulkner G, Cohn T, Remington G. Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. The Cochrane database of systematic reviews 2010(12):Cd006629.

33. Srisurapanont M, Disayavanish C, Taimkaew K. Quetiapine for schizophrenia. The Cochrane database of systematic reviews 2000(2):Cd000967.

34. American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society 2019;67(4):674-94.

35. Basciotta M, Zhou W, Ngo L, Donnino M, Marcantonio ER, Herzig SJ. Antipsychotics and the Risk of Mortality or Cardiopulmonary Arrest in Hospitalized Adults. Journal of the American Geriatrics Society 2019.

36. Gill SS, Rochon PA, Herrmann N, Lee PE, Sykora K, Gunraj N, et al. Atypical antipsychotic drugs and risk of ischaemic stroke: population based retrospective cohort study. BMJ (Clinical research ed) 2005;330(7489):445.

Material suplementar

Tabela S1 - Proporção de SGA utilizado na entrada do programa por ano.

Ano	clozapina n= 34.486	olanzapina n= 224.861	risperidona n= 251.352	quetiapina n= 251.352	ziprazidona n= 38.543	Total n= 759.654
2008	10.100 (6,5)	56.933 (36,7)	54.645 (35,20)	20.714 (13,34)	12.843 (8,27)	155.235
2009	2.077 (3,1)	19.288 (29,2)	24.520 (37,1)	15.480 (23,4)	4.692 (7,1)	66.057
2010	2.382 (3,6)	16.267 (24,6)	24.745 (37,5)	18.246 (27,6)	4.332 (6,6)	65.972
2011	2.788 (4,2)	15.153 (22,9)	26.835 (40,5)	17.568 (26,5)	3.833 (5,8)	66.177
2012	2.023 (3,6)	13.249 (23,5)	21.548 (38,2)	16.994 (30,2)	2.515 (4,5)	56.329
2013	2.271 (3,7)	16.632 (27,0)	20.437 (33,2)	19.890 (32,3)	2.293 (3,7)	61.523
2014	2.100 (3,3)	17.711 (27,9)	20.117 (31,7)	21.740 (34,3)	1.719 (2,7)	63.387
2015	3.584 (4,5)	24.664 (30,9)	21.261 (26,6)	27.977 (35,0)	2.411 (3,0)	79.897
2016	4.490 (5,6)	24.939 (31,2)	20.362 (25,5)	27.441 (34,3)	2.662 (3,3)	79.894
2017	2.671 (4,1)	20.025 (30,7)	16.882 (25,9)	24.362 (37,4)	1.243 (1,9)	65.183
Total	34.486 (5,5)	224.861(29,6)	251.352(33,2)	210.412(27,7)	38.543 (5,1)	759.654

Tabela S2 - Proporção do SGA utilizado pelas crianças/adolescentes na entrada do programa por ano.

Ano	clozapina n= 1.518	olanzapina n= 13.380	risperidona n= 43.425	quetiapina n= 8.106	ziprazidona n= 2.155	Total n= 68.584
2008	305 (2,5)	2.352 (19,3)	8.198 (67,4)	748 (6,1)	565 (4,6)	12.168
2009	99 (1,6)	1.047 (17,1)	4.155 (67,9)	588 (9,6)	227 (3,7)	6.116
2010	100 (1,6)	967 (15,3)	4.352 (68,8)	619 (9,8)	283 (4,5)	6.321
2011	127 (1,9)	961 (14,7)	4.550 (69,5)	681 (10,4)	226 (3,4)	6.545
2012	100 (1,7)	852 (14,7)	3.977 (68,6)	697 (12,0)	172 (2,9)	5.798
2013	120 (2,1)	1.132 (19,3)	3.670 (62,6)	788 (13,4)	154 (2,6)	5.864
2014	141 (2,3)	1.355 (21,9)	3.682 (59,7)	863 (13,9)	128 (2,1)	6.169
2015	185 (2,6)	1.608 (23,0)	3.982 (56,9)	1.061 (15,2)	155 (2,2)	6.991
2016	183 (2,7)	1.511 (25,6)	3.157 (53,5)	970 (16,4)	99 (1,7)	5.895
2017	105 (2.3)	1.128 (24.6)	2472 (53.9)	760 (16.6)	83 (1.8)	4584
Total	1.518 (2,2)	13.380 (19,5)	43.425 (63,3)	8.106 (11,8)	2.155 (3,1)	68.584

Tabela S3 - Proporção de SGA utilizado pelos adultos na entrada do programa por ano.

Ano	clozapina n= 30.311	olanzapina n= 177.787	risperidona n=158.415	quetiapina n=122.167	ziprazidona n=33.391	Total n = 522.071
2008	9.269 (7,8)	47.214 (39,9)	36.595 (30,9)	13.963 (11,8)	11.386 (9,6)	118.427
2009	1.817 (3,9)	15.531 (33,2)	15.079 (32,3)	10.212 (21,8)	4.111 (8,8)	46.750
2010	2.080 (4,8)	12.640 (29,0)	14.506 (33,3)	10.614 (24,4)	3.670 (8,4)	43.510
2011	2.443 (5,5)	11.875 (26,6)	16.595 (37,3)	10.298 (23,1)	3.334 (7,5)	44.545
2012	1.730 (4,6)	10.372 (27,6)	13.370 (35,6)	9.939 (26,5)	2.160 (5,6)	37.571
2013	1.953 (4,8)	12.994 (31,6)	12.735 (31,0)	11.398 (27,8)	1.979 (4,8)	41.059
2014	1.774 (4,3)	13.498 (32,8)	12.456 (30,3)	11.984 (29,1)	1.450 (3,5)	41.162
2015	3.106 (5,8)	19.029 (35,7)	13.359 (25,1)	15.790 (29,6)	2.033 (3,8)	53.317
2016	3.865 (7,2)	19.215 (35,8)	13.050 (24,3)	15.304 (28,5)	2.244 (4,2)	53.678
2017	2.274 (5,4)	15.419 (36,7)	10.670 (25,4)	12.665 (30,1)	1.024 (2,4)	42.052
Total	30.311(5,8)	177.787(34,1)	158.415 (30,3)	122.167 (23,4)	33.391(6,4)	522.071

Tabela S4 - Proporção do SGA utilizado pelos idosos na entrada do programa por ano.

Ano	clozapina n= 2.657	olanzapina n=33.694	risperidona n=49.512	Quetiapina n=80.139	ziprazidona n= 2.997	Total n= 168.999
2008	526 (2,1)	7.367 (29,9)	9.852 (39,9)	6.003 (24,4)	892 (3,6)	24.640
2009	161 (1,2)	2.710 (20,5)	5.286 (40,1)	4.680 (35,5)	354 (2,7)	13.191
2010	202 (1,2)	2.660 (16,5)	5.887 (36,5)	7.013 (43,4)	379 (2,3)	16.141
2011	218 (1,4)	2.317 (15.4)	5.690 (37,7)	6.589 (43,7)	273 (1,8)	15.087
2012	193 (1,5)	2.025 (15,6)	4.201 (32,4)	6.358 (49,1)	183 (1,4)	12.960
2013	198 (1,4)	2.506 (17,2)	4.032 (27,6)	7.704 (52,77)	160 (1,1)	14.600
2014	185 (1,1)	2.858 (17,8)	3.979 (24,8)	8.893 (55,4)	141 (0,9)	16.056
2015	293 (1,5)	4.027 (20,6)	3.920 (20,0)	11.126 (56,8)	223 (1,1)	19.589
2016	442 (2,3)	4.129 (21,2)	3.610 (18,5)	11.046 (56,6)	272 (1,4)	19.499
2017	239 (1,4)	3.095 (17,9)	3.055 (17,7)	10.727 (62,2)	120 (0,7)	17.236
Total	2.657 (1,6)	33.694 (19,9)	49.512 (29,3)	80.139 (47,4)	2.997 (1,8)	168.999

6 CONSIDERAÇÕES FINAIS

O uso das ferramentas da tradução do conhecimento revelou que o processo de desinstitucionalização no Brasil ainda apresenta importantes deficiências para sua consolidação. As principais barreiras incluem ausência de estratégias baseadas em evidências, escassez de profissionais devidamente qualificados em saúde mental, número insuficiente de serviços comunitários, carência de recursos financeiros e apoio político e falta de integração entre os serviços, especialmente com a atenção primária. Apesar de algumas políticas de saúde mental serem bem desenhadas, estas não estão totalmente implementadas. A instabilidade política e as alterações recentes ocorridas na legislação mostram pontos de conflitos e discrepâncias desde a reforma psiquiátrica.

Por meio de uma grande base de dados administrativos (SIA/SUS), este estudo também traçou o cenário no mundo real quanto a utilização de SGA em pacientes com esquizofrenia e transtorno esquizoafetivo atendidos pelo SUS e trouxe importantes achados para a saúde pública. A maioria dos pacientes em tratamento com SGA assistidos pelo SUS eram adultos, com esquizofrenia paranoide e residentes na região sudeste. Os SGA mais prescritos foram a risperidona e a olanzapina, sendo observadas diferenças no padrão de uso de acordo com a faixa etária. Crianças e adolescentes utilizaram mais risperidona; adultos, olanzapina e; os idosos, quetiapina.

Verificou-se que uma parcela considerável de crianças e adolescentes utilizavam SGA que não são aprovados para tratamento da esquizofrenia nessa faixa etária no Brasil. Risperidona, olanzapina e quetiapina são aprovados somente a partir de 13 anos de idade e a clozapina e ziprasidona, não são aprovados, pois até o momento não tem eficácia e segurança comprovada.

Apesar da controvérsia existente na literatura sobre a diferença de sexo entre os pacientes com esquizofrenia, as crianças e adolescentes aqui investigadas, exibiram diferenças importantes relacionadas ao predomínio do sexo masculino.

Foi constatado que a maioria dos pacientes adultos trocaram pelo menos uma vez o SGA ao longo do tratamento, cujos fatores associados à troca foram sexo feminino, idade avançada e diagnóstico de transtorno esquizoafetivo. Os usuários de risperidona tiveram maior frequência de trocas, e os usuários de clozapina tiveram menor frequência de trocas.

Em um país com recursos escassos como o Brasil, o desenvolvimento de síntese de evidências e de estudos de utilização de medicamentos são necessários, a fim de diminuir a lacuna existente entre a prática clínica e a produção científica, e promover desfechos positivos na saúde de sua população. A troca de SGA pode acarretar maior custo ao sistema de saúde, maior exposição a potenciais efeitos adversos, interações medicamentosas graves e toxicidade, além de aumentar o risco de desestabilização, crises e hospitalizações. Por esses motivos, sugere-se que maior atenção deva ser dada às crianças e idosos, grupos que são mais vulneráveis aos efeitos dos SGA, além da implementação de protocolos clínicos específicos para os extremos etários é necessária.

Melhorar o cuidado e o tratamento prestado aos pacientes com transtornos mentais é um dos maiores desafios da saúde pública. Os resultados deste estudo poderiam ser ampliados com a possibilidade de pareamento com outras bases de dados brasileiras, tais como o Sistema de Informações Hospitalares e com o Sistema de Informações sobre Mortalidade, a fim de fornecer desfechos mais importantes. No entanto, ainda a política de acesso ao dado no Brasil tem muito a evoluir no sentido da transparência no acesso e pareamento entre as bases.

As estratégias de tradução do conhecimento utilizadas nos estudos aqui produzidos (síntese de evidências, diálogo deliberativo e dados sobre utilização de antipsicóticos no Brasil) podem ser ferramentas valiosas na construção de políticas públicas para melhorar o cuidado de pacientes com transtornos mentais, diminuir as inequidades e as fragilidades do sistema.

O uso de dados de mundo real devidamente validados subsidia políticas públicas robustas e consolidam o sistema de saúde. A disponibilização de bases de dados para acesso livre a pesquisadores e a relação estreita entre academia e gestão podem ampliar o diálogo, favorecer pesquisas para a tomada de decisão, ampliar os fluxos de conhecimento entre os diferentes órgãos públicos de decisão, e ainda contribuir na formulação de políticas públicas para a produção de serviços de saúde e melhores desfechos para os cidadãos.

REFERÊNCIAS

1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2016 (GBD 2016) results. [acesso em 20 out 2019]. Disponível em: http://ghdx.healthdata.org/gbd-results-tool.

2. Santos EG, Siqueira MM. Prevalência dos transtornos mentais na população adulta brasileira: uma revisão sistemática de 1997 a 2009. J Jornal Brasileiro de Psiquiatria 2010;59:238-46.

3. Whiteford HA, Degenhardt L, Rehm J, Baxter AJ, Ferrari AJ, Erskine HE, et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet (London, England) 2013;382(9904):1575-86.

4. Bonadiman CSC, Passos VMdA, Mooney M, Naghavi M, Melo APS. A carga dos transtornos mentais e decorrentes do uso de substâncias psicoativas no Brasil: Estudo de Carga Global de Doença, 1990 e 2015. J Revista Brasileira de Epidemiologia 2017;20:191-204.

5. GBD 2016 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet (London, England) 2016;388(10053):1545-602.

6. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégicas. Coordenação Geral de Saúde Mental. Reforma psiquiátrica e política de saúde mental no Brasil. Documento apresentado à Conferência Regional de Reforma dos Serviços de Saúde Mental : 15 anos depois de Caracas. Brasília: Organização Pan-Americana de Saúde; 2005.

7. Amarante P, Nunes MO. A reforma psiquiátrica no SUS e a luta por uma sociedade sem manicômios. J Ciência & Saúde Coletiva 2018;23:2067-74.

8. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde/DAPE. Saúde Mental em Dados 7 (Edição Especial). Ano V, nº 7. Informativo eletrônico. Brasília: 2010. [acesso em 10 set. 2018]. Disponível em: http://portal.saude.gov.br/portal/arquivos/pdf/smdados.pdf

9. Brasil. Lei n° 10.216, de 6 de abril de 2001. Dispõe sobre a proteção e os direitos das pessoas portadoras de transtornos mentais e redireciona o modelo assistencial em saúde mental. [acesso em 26 nov.2020]. Disponível em: www.planalto.gov.br/ccivil_03/Leis?LEIS_2001/L10216.htm

10. Jorge MR, França JM. A Associação Brasileira de Psiquiatria e a Reforma da Assistência Psiquiátrica no Brasil. J Brazilian Journal of Psychiatry 2001;23:3-6.

11. Silva PRF, Carvalho MCA, Cavalcanti MT, Echebarrena RC, Mello ASd, Dahl CM, et al. Desinstitucionalização de pacientes de longa permanência de um hospital psiquiátrico no Rio de Janeiro. Ciência & Saúde Coletiva 2017;22:2341-52.

12. Vidal CEL, Bandeira M, Gontijo ED. Reforma psiquiátrica e serviços residenciais terapêuticos. Jornal Brasileiro de Psiquiatria 2008;57:70-9.

13. Fagundes Júnior HM, Desviat M, Silva PRF. Reforma Psiquiátrica no Rio de Janeiro: situação atual e perspectivas futuras. J Ciência & Saúde Coletiva. 2016;21:1449-60.

14. National Collaborating Centre for Mental Health. National Institute for Health and Clinical Excellence Guidance. Psychosis and schizophrenia in adults: treatment and management. [acessado em 25 set. 2019]. Disponível em: nice.org.uk/guidance/cg178/evidence/full-guideline-490503565

15. Bota RG, Preda A. Schizoaffective disorder. BMJ Best Practice (última atualização em maio 2018). [acessado em 19 nov. 2019]. Disponível em: https://bestpractice-bmj-com.libaccess.lib.mcmaster.ca/topics/en-gb/1199/pdf/1199.pdf

16. Kilsztajn S, Lopes EdS, Lima LZ, Rocha PAFd, Carmo MSNd. Leitos hospitalares e reforma psiquiátrica no Brasil. J Cadernos de Saúde Pública 2008;24:2354-62.

17. Preda A, Bota RG. Esquizofrenia. BMJ Best Practice (última atualização em 2019). [acessado em 19 nov. 2019]. Disponível em: bestpractice.bmj.com/topics/pt-br/406/pdf/406/Esquizofrenia.pdf

18. Saha KB, Bo L, Zhao S, Xia J, Sampson S, Zaman RU. Chlorpromazine versus atypical antipsychotic drugs for schizophrenia. The Cochrane database of systematic reviews 2016;4(4):Cd010631.

19. Graham ID, Logan J, Harrison MB, Straus SE, Tetroe J, Caswell W, et al. Lost in knowledge translation: time for a map? The Journal of continuing education in the health professions 2006;26(1):13-24.

20. Dias RI, Barreto JOM, Souza NM. Desenvolvimento atual da Rede de Políticas Informadas por Evidências (EVIPNet Brasil): relato de caso. Rev Panam Salud Publica 2014;36(1):50-6.

21. Ongolo-Zogo P, Lavis JN, Tomson G, Sewankambo NK. Assessing the influence of knowledge translation platforms on health system policy processes to achieve the health millennium development goals in Cameroon and Uganda: a comparative case study. Health policy and planning 2018;33(4):539-54.

22. Organização Pan-Americana de Saúde. Como EVIPNet apoia a utilização de conhecimento científico na tomada de decisão política em saúde? [acessado em 10 nov 2019]. Disponível em: https://www.paho.org/bra/index.php?option=com_content&view=article&id=3143:com

o-evipnet-apoia-a-utilizacao-de-conhecimento-cientifico-na-tomada-de-decisao-politica-em-saude&Itemid=838

23. Lavis JN, Oxman AD, Lewin S, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP). Health research policy and systems 2009;7 (Suppl 1):I1.

24. Rede para Políticas Informadas por Evidências. Sobre EVIPNet Brasil. [acessado em 22 nov 2019]. Disponível em: http://brasil.evipnet.org

25. Lavis JN, Permanand G, Oxman AD, Lewin S, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP) 13: Preparing and using policy briefs to support evidence-informed policymaking. Health research policy and systems 2009;7 Suppl 1:S13.

26. Lavis JN, Boyko JA, Oxman AD, Lewin S, Fretheim A. SUPPORT Tools for evidence-informed health Policymaking (STP) 14: Organising and using policy dialogues to support evidence-informed policymaking. Health research policy and systems 2009;7 Suppl 1:S14.

27. Dias RISC, Barreto JOM, Vanni T, Candido AMSC, Moraes LH, Gomes MAR. Estratégias para estimular o uso de evidências científicas na tomada de decisão. J Cadernos Saúde Coletiva 2015;23:316-22.

28. Malla C, Aylward P, Ward P. Knowledge translation for public health in low- and middle- income countries: a critical interpretive synthesis. Global health research and policy 2018;3:29.

29. Garcia M. A mortalidade nos manicômios da região de Soroccaba e a possibilidade da investigação de violação de direitos humanos no campo da saúde mental por meio do acesso aos bancos de dados públicos. Rev Psicologia Política 2012;12:105-20.

30. Emerich BF, Yasui S. O hospital psiquiátrico em diálogos atemporais. J Interface - Comunicação, Saúde, Educação. 2016;20:207-16.

31. Lamb HR, Bachrach LL. Some perspectives on deinstitutionalization. Psychiatric services (Washington, DC) 2001;52(8):1039-45.

32. Bachrach LL. The state of the state mental hospital at the turn of the century. New directions for mental health services 1999(84):7-24.

33. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Ações Programáticas Estratégicas. Coordenação Geral de Saúde Mental, Álcool e Outras Drogas. Saúde Mental em Dados – 12, Ano 10, nº 12. Brasília: Informativo eletrônico de dados sobre a Política Nacional de Saúde Mental, 2015, 48p. [acessado em 06 jan 2017]. Disponível em: http://www.mhinnovation.net/sites/default/files/downloads/innovation/reports/Report_12-edicao-do-Saude-Mental-em-Dados.pdf

34. Sorocaba. Prefeitura de Sorocaba. Hospital Vera Cruz tem quinta alta médica no ano. [acessado em 26 out 2020]. Disponível em: http://agencia.sorocaba.sp.gov.br/hospital-vera-cruz-tem-quinta-alta-medica-no-ano/

35. Ziguras SJ, Stuart GW. A meta-analysis of the effectiveness of mental health case management over 20 years. Psychiatric services (Washington, DC) 2000;51(11):1410-21.

36. Machado LF, Dahl CM, Carvalho MCA, Cavalcanti MT. Programa de tratamento assertivo na comunidade (PACT) e gerenciamento de casos (case management): revisão de 20 anos da literatura. Jornal Brasileiro de Psiquiatria 2007;56:208-18.

37. Ryu Y, Mizuno M, Sakuma K, Munakata S, Takebayashi T, Murakami M, et al. Deinstitutionalization of long-stay patients with schizophrenia: the 2-year social and clinical outcome of a comprehensive intervention program in Japan. The Australian and New Zealand journal of psychiatry 2006;40(5):462-70.

38. Amarante P, Torre EHG. De volta à cidade, sr. cidadão! - reforma psiquiátrica e participação social: do isolamento institucional ao movimento antimanicomial. J Revista de Administração Pública 2018;52:1090-107.

39. Stahl SM. Psicofarmacologia: bases neurocientíficas e aplicações práticas. 4 ed. Rio de Janeiro: Guanabara Koogan; 2014.

40. American Geriatrics Society. American Geriatrics Society 2019 Updated AGS Beers Criteria(R) for Potentially Inappropriate Medication Use in Older Adults. Journal of the American Geriatrics Society 2019;67(4):674-94.

41. DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. *T115234*, *Schizophrenia*; [atualizado em 30 Nov *2018*]. Disponível em: https://www.dynamed.com/topics/dmp~AN~T115234.

42. Aleman A, Kahn RS, Selten JP. Sex differences in the risk of schizophrenia: evidence from meta-analysis. Archives of general psychiatry 2003;60(6):565-71.

43. Takahashi S, Matsuura M, Tanabe E, Yara K, Nonaka K, Fukura Y, et al. Age at onset of schizophrenia: gender differences and influence of temporal socioeconomic change. Psychiatry and clinical neurosciences 2000;54(2):153-6.

44. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 5. ed. (DSM-5). Washington, DC: American Psychiatric Publishing; 2013.

45. Alves CRR, Silva MTA. A esquizofrenia e seu tratamento farmacológico. J Estudos de Psicologia (Campinas) 2001;18:12-22.

46. Dos Reis GC, Arruda ALA. Fisiopatologia da esquizofrenia baseada nos aspectos moleculares da hipótese glutamatérgica. Rev Bras Farm 2011;92(3):118-22.

47. DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 - . Record No. *T115778*, *Schizoaffective Disorder*; [atualizado 30 nov 2018]. Disponível em: https://www.dynamed.com/topics/dmp~AN~T115778

48. Brasil. Ministério da Saúde. Secretaria de atenção à saúde. Protocolo Clínico e Diretrizes Terapêuticas do Transtorno Esquizoafetivo. Brasília: Ministério da Saúde, 2014. 33p.

49. Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, Duggan L, et al. Olanzapine versus other atypical antipsychotics for schizophrenia. The Cochrane database of systematic reviews 2010(3):Cd006654.

50. Raben AT, Marshe VS, Chintoh A, Gorbovskaya I, Muller DJ, Hahn MK. The Complex Relationship between Antipsychotic-Induced Weight Gain and Therapeutic Benefits: A Systematic Review and Implications for Treatment. Frontiers in neuroscience 2017;11:741.

51. De Berardis D, Rapini G, Olivieri L, Di Nicola D, Tomasetti C, Valchera A, et al. Safety of antipsychotics for the treatment of schizophrenia: a focus on the adverse effects of clozapine. Therapeutic advances in drug safety 2018;9(5):237-56.

52. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the Pharmacotherapy of Schizophrenia in Adults. Canadian journal of psychiatry Revue canadienne de psychiatrie 2017;62(9):604-16.

53. Hui CLM, Lam BST, Lee EHM, Chan SKW, Chang WC, Suen YN, et al. A systematic review of clinical guidelines on choice, dose, and duration of antipsychotics treatment in first- and multi-episode schizophrenia. International review of psychiatry (Abingdon, England) 2019;31(5-6):441-59.

54. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM. Maintenance treatment with antipsychotic drugs for schizophrenia. The Cochrane database of systematic reviews 2012(5):Cd008016.

55. Siskind D, McCartney L, Goldschlager R, Kisely S. Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. The British journal of psychiatry: the journal of mental science 2016;209(5):385-92.

56. Asenjo Lobos C, Komossa K, Rummel-Kluge C, Hunger H, Schmid F, Schwarz S, et al. Clozapine versus other atypical antipsychotics for schizophrenia. The Cochrane database of systematic reviews 2010(11):Cd006633.

57. Asmal L, Flegar SJ, Wang J, Rummel-Kluge C, Komossa K, Leucht S. Quetiapine versus other atypical antipsychotics for schizophrenia. The Cochrane database of systematic reviews 2013(11):Cd006625.

58. Komossa K, Rummel-Kluge C, Hunger H, Schwarz S, Bhoopathi PS, Kissling W, et al. Ziprasidone versus other atypical antipsychotics for schizophrenia. The Cochrane database of systematic reviews 2009(4):Cd006627.

59. Komossa K, Rummel-Kluge C, Schwarz S, Schmid F, Hunger H, Kissling W, et al. Risperidone versus other atypical antipsychotics for schizophrenia. The Cochrane database of systematic reviews 2011(1):Cd006626.

60. Ringback Weitoft G, Berglund M, Lindstrom EA, Nilsson M, Salmi P, Rosen M. Mortality, attempted suicide, re-hospitalisation and prescription refill for clozapine and other antipsychotics in Sweden-a register-based study. Pharmacoepidemiology and drug safety 2014;23(3):290-8.

61. Keating D, McWilliams S, Schneider I, Hynes C, Cousins G, Strawbridge J, et al. Pharmacological guidelines for schizophrenia: a systematic review and comparison of recommendations for the first episode. BMJ open 2017;7(1):e013881.

62. Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. The Australian and New Zealand journal of psychiatry 2016;50(5):410-72.

63. Scottish Intercollegiate Guidelines Network. Management of schizophrenia. Edinburgh: SIGN; 2013. Disponível em: http://www.sign.ac.uk/assets/sign131.pdf.

64. Osser DN, Roudsari MJ, Manschreck T. The psychopharmacology algorithm project at the Harvard South Shore Program: an update on schizophrenia. Harvard review of psychiatry 2013;21(1):18-40.

65. Kane JM, Leucht S, Carpenter D, Docherty JP. The expert consensus guideline series. Optimizing pharmacologic treatment of psychotic disorders. Introduction: methods, commentary, and summary. The Journal of clinical psychiatry 2003;64 Suppl 12:5-19.

66. Royal College of Psychiatrists. Consensus Statement on High-Dose Antipsychotic
Medication. London: Royal College of Psychiatrists; 2006.

67. Munoz-Negro JE, Cuadrado L, Cervilla JA. Current Evidences on Psychopharmacology of Schizoaffective Disorder. Actas espanolas de psiquiatria 2019;47(5):190-201.

68. Brasil. Ministério da Saúde. Secretaria de atenção à saúde. Protocolo Clínico e Diretrizes Terapêuticas. Esquizofrenia refratária. Brasília: Ministério da Saúde, 2002. 10 p.

69. Brasil. Ministério da Saúde. Secretaria de atenção à saúde. Protocolo Clínico e Diretrizes Terapêuticas. Esquizofrenia refratária. Brasília: Ministério da Saúde, 2013. 42p.

70. Kennedy E, Kumar A, Datta SS. Antipsychotic medication for childhood-onset schizophrenia. The Cochrane database of systematic reviews 2007;2007(3):Cd004027.

71. Kumar A, Datta SS, Wright SD, Furtado VA, Russell PS. Atypical antipsychotics for psychosis in adolescents. The Cochrane database of systematic reviews 2013(10):Cd009582.

72. Essali A, Ali G. Antipsychotic drug treatment for elderly people with late-onset schizophrenia. The Cochrane database of systematic reviews 2012(2):Cd004162.

73. Abidi S, Mian I, Garcia-Ortega I, Lecomte T, Raedler T, Jackson K, et al. Canadian Guidelines for the Pharmacological Treatment of Schizophrenia Spectrum and Other Psychotic Disorders in Children and Youth. Canadian journal of psychiatry Revue canadienne de psychiatrie 2017;62(9):635-47.

74. National Collaborating Centre for Mental Health. National Institute for Health and Clinical Excellence: Guidance. Psychosis and Schizophrenia in Children and Young People: Recognition and Management. Leicester (UK): British Psychological Society and The Royal College of Psychiatrists, 2013.

75. McClellan J, Stock S. Practice parameter for the assessment and treatment of children and adolescents with schizophrenia. Journal of the American Academy of Child and Adolescent Psychiatry 2013;52(9):976-90.

76. KLASCO RK, editor. DRUGDEX System [Database on the Internet].Greenwood Village (Colorado): Thomson Micromedex; [1974-2019]. Disponível em: https://www-micromedexsolutions-com

77. Agência Nacional de Vigilância Sanitária. Bulário eletrônico [acesso em 10 nov 2020] Disponível em: https://consultas.anvisa.gov.br/#/bulario

78. British National Formulary. British National Formulary for children 2019-2020 [acesso em 10 out 2020]. Disponível em: bnfc.nice.org.uk

79. Hsu CW, Lee SY, Wang LJ. Gender differences in the prevalence, comorbidities and antipsychotic prescription of early-onset schizophrenia: a nationwide population-based study in Taiwan. European child & adolescent psychiatry 2019;28(6):759-67.

80. Chen W, Cepoiu-Martin M, Stang A, Duncan D, Symonds C, Cooke L, et al. Antipsychotic Prescribing and Safety Monitoring Practices in Children and Youth: A Population-Based Study in Alberta, Canada. Clinical drug investigation 2018;38(5):449-55.

81. Lao KSJ, Tam AWY, Wong ICK, Besag FMC, Man KKC, Chui CSL, et al. Prescribing trends and indications of antipsychotic medication in Hong Kong from 2004 to 2014: General and vulnerable patient groups. Pharmacoepidemiology and drug safety 2017;26(11):1387-94.

82. Curtis LH, Masselink LE, Østbye T, Hutchison S, Dans PE, Wright A, et al. Prevalence of atypical antipsychotic drug use among commercially insured youths in the United States. Archives of pediatrics & adolescent medicine 2005;159(4):362-6.

83. Schröder C, Dörks M, Kollhorst B, Blenk T, Dittmann RW, Garbe E, et al. Outpatient antipsychotic drug use in children and adolescents in Germany between 2004 and 2011. European child & adolescent psychiatry 2017;26(4):413-20.

84. Basciotta M, Zhou W, Ngo L, Donnino M, Marcantonio ER, Herzig SJ. Antipsychotics and the Risk of Mortality or Cardiopulmonary Arrest in Hospitalized Adults. Journal of the American Geriatrics Society 2020;68(3):544-550.

85. Tessier A, Boyer L, Husky M, Bayle F, Llorca PM, Misdrahi D. Medication adherence in schizophrenia: The role of insight, therapeutic alliance and perceived trauma associated with psychiatric care. Psychiatry research 2017;257:315-21.

86. Cramer JA, Rosenheck R. Compliance with medication regimens for mental and physical disorders. Psychiatric services (Washington, DC) 1998;49(2):196-201.

87. Garcia S, Martinez-Cengotitabengoa M, Lopez-Zurbano S, Zorrilla I, Lopez P, Vieta E, et al. Adherence to Antipsychotic Medication in Bipolar Disorder and Schizophrenic Patients: A Systematic Review. Journal of clinical psychopharmacology 2016;36(4):355-71.

88. Faries DE, Ascher-Svanum H, Nyhuis AW, Kinon BJ. Clinical and economic ramifications of switching antipsychotics in the treatment of schizophrenia. BMC psychiatry 2009;9:54.

89. Nyhuis AW, Faries DE, Ascher-Svanum H, Stauffer VL, Kinon BJ. Predictors of switching antipsychotic medications in the treatment of schizophrenia. BMC psychiatry 2010;10:75.

90. Masand PS. A review of pharmacologic strategies for switching to atypical antipsychotics. Primary care companion to the Journal of clinical psychiatry 2005;7(3):121-9.

91. Barbosa WB, Costa JO, de Lemos LLP, Gomes RM, de Oliveira HN, Ruas CM, et al. Costs in the Treatment of Schizophrenia in Adults Receiving Atypical Antipsychotics: An 11-Year Cohort in Brazil. Applied health economics and health policy 2018;16(5):697-709.

92. National Health Service. Guidelines for Antipsychotic Medication Switches. [acesso em 20 dez 2018]. Disponível em: nhs_guidelines_antipsychotic_switch.pdf (psychdb.com)

93. Hatta K, Sugiyama N, Ito H. Switching and augmentation strategies for antipsychotic medications in acute-phase schizophrenia: latest evidence and place in therapy. Therapeutic advances in psychopharmacology 2018;8(6):173-83.

94. Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. Journal of clinical epidemiology 2005;58(4):323-37.

95. Herrett E, Thomas SL, Schoonen WM, Smeeth L, Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. British journal of clinical pharmacology 2010;69(1):4-14.

96. Ali MS, Ichihara MY, Lopes LC, Barbosa GCG, Pita R, Carreiro RP, et al. Administrative Data Linkage in Brazil: Potentials for Health Technology Assessment. Frontiers in pharmacology 2019;10:984.

97. Brasil. Departamento de Informática do Sistema Único de Saúde. [acessado em 10 maio 2020]. Disponível em: http://datasus.saude.gov.br

98. Rede Interagencial de Informação para a Saúde Indicadores básicos para a saúde no Brasil: conceitos e aplicações / Rede Interagencial de Informação para a Saúde – Ripsa. 2. ed. Brasília: Organização Pan-Americana da Saúde, 2008. 349 p.

99. Brasil. Portaria nº 1.554, de 30 de julho de 2013. Dispõe sobre as regras de financiamento e execução do componente especializado da assistência Farmacêutica no âmbito do Sistema Único de Saúde (SUS). [acesso em 9 jul 2018]. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2013/prt1554_30_07_2013.html

100. BRASIL. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Departamento de Assistência Famacêutica e Insumos Estratégicos. Da excepcionalidade às linhas de cuidado: o Componente Especializado da Assistência Farmacêutica. Brasília: Ministério da Saúde, 2010. 262 p.

101. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Portaria nº. 768, de 26 de outubro de 2006. Diário Oficial da União, Poder Executivo, Brasília, DF, 27 de outubro de 2006.

102. Soares C, Silva GA. Uso de registros de assistência farmacêutica do Sistema de Informações Ambulatorial para avaliação longitudinal de utilização e adesão a medicamentos. J Cadernos Saúde Coletiva 2013;21:245-52.

103. Machado MAA, Moura CS, Ferré F, Bernatsky S, Rahme E, Acurcio FA. Treatment persistence in patients with rheumatoid arthritis and ankylosing spondylitis. J Revista de Saúde Pública 2016;50.

ANEXO A - ORIENTAÇÕES PARA APRESENTAÇÃO DE TESES DO PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS FARMACÊUTICAS DA UNIVERSIDADE DE SOROCABA

UNISO
Programa de Pós-Graduação em Ciências Farmacêuticas

Orientações para apresentação de dissertações/teses do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba

As dissertações/teses do Programa de Pós-Graduação em Ciências Farmacêuticas da Universidade de Sorocaba (PPGCF-Uniso) poderão ser apresentadas em dois formatos: o tradicional ou em formato de artigo(s) científico(s).

Os trabalhos de investigação que possam resultar em patentes poderão ser apresentados na forma convencional, a critério do grupo de pesquisadores envolvidos, reservadas as particularidades exigidas em relação ao sigilo.

O formato tradicional segue o padrão descrito nas normas do "Manual para normalização de trabalhos acadêmicos" da Universidade de Sorocaba.

As dissertações entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de **pelo menos um** artigo em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e podem ser inseridos no idioma e na formatação estabelecida pelo(s) respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

As teses entregues no formato de artigo científico têm como exigência a publicação ou, no mínimo, a submissão prévia de **pelo menos dois artigos** em revista científica com classificação mínima Qualis/Capes B2 (de acordo com a categorização da WebQualis mais recente, na data do envio/publicação) e podem ser inseridos no idioma e na formatação estabelecida pelo(s) respectivo(s) periódico(s). Os demais artigos podem não ter sido submetidos ainda.

Para aclarar membros da banca que desconhecem esta versão alternativa da dissertação/tese recomenda-se anexar este documento no final das versões encaminhadas aos membros da banca.

A dissertação/tese no formato de artigo(s) científico(s) deverá possuir os elementos apresentados no Quadro 1.

Quadro 1 - Elementos para a construção da dissertação no formato de artigo(s) científico(s).

Elementos pré-textuais	*1. Folha de rosto*
	2. Errata (Opcional)
	3. Folha de aprovação
	4. Dedicatória (Opcional)
	5. Agradecimentos (Opcional)
	6. Epígrafe (Opcional)
	7. Resumo na língua vernácula

UNISO
Programa de Pós-Graduação em Ciências Farmacêuticas

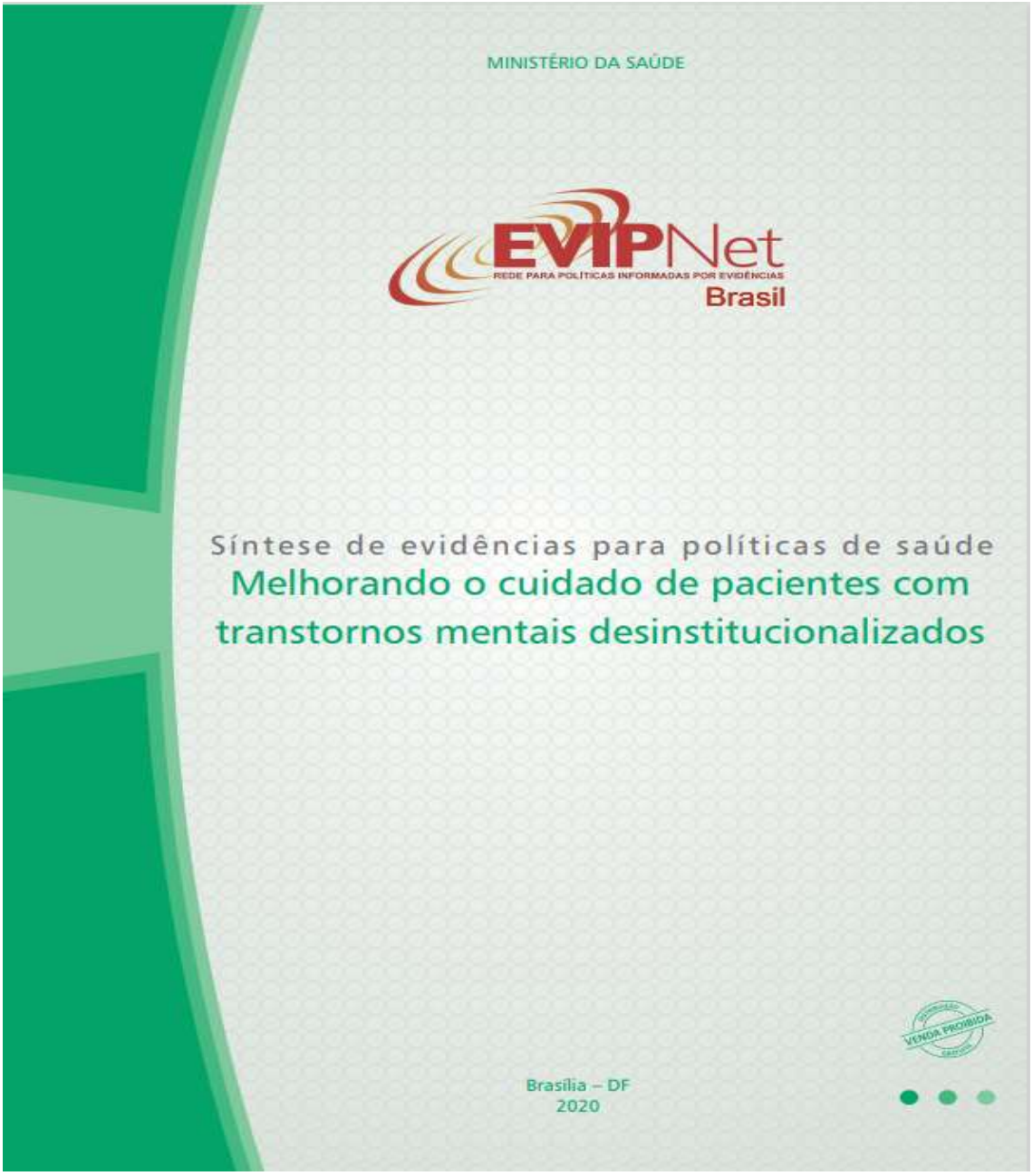
	8. Resumo em inglês (Abstract)
	9. Lista de abreviaturas e siglas; lista de tabelas e lista de símbolos (opcionais). Estas listas não devem conter as informações apresentadas nos artigos científicos.
	10. Sumário
Elementos textuais	*11. Introdução ou apresentação:* trata-se da parte inicial do texto com formulação clara e simples do tema investigado, constando a delimitação do assunto tratado, sua relevância e justificativa.
	12. Revisão de literatura: quando a revisão de literatura for concebida como artigo de revisão, este item deverá ser incluído no item resultado(s).
	13. Objetivos: geral e específico
	14. Material e Métodos (opcional). Quando parte dos resultados não for apresentada no formato de artigo, este item deverá ser incluído após os objetivos específicos. Quando o autor quiser apresentar o(s) método(s) de forma mais detalhada do que no artigo, este item pode também ser apresentado em separado.
	15. Resultados (pode ser apresentado no formato de artigos): deve(m) ser inserida(s) a(s) cópia(s) de artigo(s) derivado(s) da dissertação, previamente publicados, submetidos ou não para publicação em revistas científicas. Sugere-se que cada artigo seja antecedido de uma breve apresentação seguida dos elementos de identificação do artigo (autores, título, revista de publicação, volume, páginas). Os artigos anexados poderão ser apresentados nos formatos exigidos pelas revistas, as quais os artigos foram publicados e/ou submetidos. Parte dos resultados pode ser apresentada em separado dos artigos, quando conveniente.
	16. Discussão (opcional): O autor pode ampliar a discussão dos resultados, quando conveniente.
	17. Conclusão ou Considerações finais: esta parte deverá conter a conclusão do trabalho ou as considerações do autor sobre os resultados alcançados frente aos objetivos propostos.

UNISO

Programa de Pós-Graduação em Ciências Farmacêuticas

Elementos pós-textuais	*18. Referências:* Devem seguir as normas do "Manual para normalização de trabalhos acadêmicos" da Universidade de Sorocaba. Não devem ser inseridas as referências apresentadas nos artigos.
	19. Apêndices (Opcional)
	20. Anexos (Opcional)

ANEXO B – PUBLICAÇÃO DO LIVRO



ANEXO C – PUBLICAÇÃO DO ARTIGO CIENTÍFICO 1

frontiers in Pharmacology

POLICY AND PRACTICE REVIEWS
published: 21 January 2020
doi: 10.3389/fphar.2019.01470

Knowledge Translation for Improving the Care of Deinstitutionalized People With Severe Mental Illness in Health Policy

*Izabela Fulone[1], Jorge Otavio Maia Barreto[2], Silvio Barberato-Filho[1], Marcel Henrique de Carvalho[3] and Luciane Cruz Lopes[1]**

[1] Pharmaceutical Sciences Graduate Course, University of Sorocaba, UNISO, Sorocaba, Brazil, [2] Ficoruz School of Government, Ficoruz Brasília, Oswaldo Cruz Foundation, Brasília, Brazil, [3] Veredas Institute, Brasília, Brazil

OPEN ACCESS

Edited by:
Iris Hoxha,
University of Medicine, Tirana, Albania

Reviewed by:
Adina Turcu-Stiolica,
University of Medicine and Pharmacy of Craiova, Romania
Kurt Neumann,
Independent Researcher, Kerékteleki, Hungary

***Correspondence:**
Luciane Cruz Lopes
luciane.lopes@prof.uniso.br; luslopesbr@gmail.com

Specialty section:
This article was submitted to Pharmaceutical Medicine and Outcomes Research, a section of the journal Frontiers in Pharmacology

Received: 02 August 2019
Accepted: 13 November 2019
Published: 21 January 2020

Citation:
Fulone I, Barreto JOM, Barberato-Filho S, Carvalho MH, and Lopes LC (2020) Knowledge Translation for Improving the Care of Deinstitutionalized People With Severe Mental Illness in Health Policy. Front. Pharmacol. 10:1470. doi: 10.3389/fphar.2019.01470

Background: Knowledge translation (KT) is an effective strategy that uses the best available research evidence to bring stakeholders together to develop solutions and improve public health policy-making. Despite progress, the process of deinstitutionalization in Brazil is still undergoing consolidation, and the changes and challenges that are involved in this process are complex and necessitate evidence-informed decision-making. Accordingly, this study used KT tools to support efforts that aim to improve the care that is available to deinstitutionalized people with severe mental disorders in Brazil.

Methods: We used the Supporting Policy Relevant Reviews and Trials tools for evidence-informed health policymaking and followed eight steps: 1) capacity building; 2) identification of a priority policy issue within a Brazilian public health system; 3) meetings with policy-makers, researchers and stakeholders; 4) development of an evidence brief (EB) that addresses the problem of deinstitutionalization; 5) facilitating policy dialogue (PD); 6) the evaluation of the EB and PD; 7) post-dialogue mini-interviews; and 8) dissemination of the findings.

Results: Capacity building and meetings with key informants promoted awareness about the gap between research and practice. Local findings were used to define the problem and develop the EB. Twenty-four individuals (policy-makers, stakeholders, researchers, representatives of the civil society, and public defense) participated in the PD. They received the EB to subsidise their deliberations during the PD, which in turn were used to validate and improve the EB. The PD achieved the objective of promoting an exhaustive discussion about the problem and proposed options and improved communication and interaction among those who are involved in mental health care. The features of both the EB and PD were considered to be favorable and helpful.

Conclusions: The KT strategy helped participants understand different perspectives and values, the interpersonal tensions that exist among those who are involved in the field of

ANEXO D – COMPROVANTE DE SUBMISSÃO DO ARTIGO CIENTÍFICO 2

frontiers

IMPROVING CARE FOR DEINSTITUTIONALIZED PEOPLE WITH MENTAL DISORDERS: EXPERIENCES OF THE USE OF KNOWLEDGE TRANSLATION TOOLS

IZABELA FULONE[1], Jorge O. Barreto[2], Silvio Barberato-Filho[1], Cristiane D. Bergamaschi[1], Marcus T. Silva[1], Luciane C. Lopes[1*]

[1]Universidade de Sorocaba, Brazil, [2]Fiocruz Government School, Brazil

Submitted to Journal:
Frontiers in Psychiatry

Specialty Section:
Public Mental Health

Article type:
Original Research Article

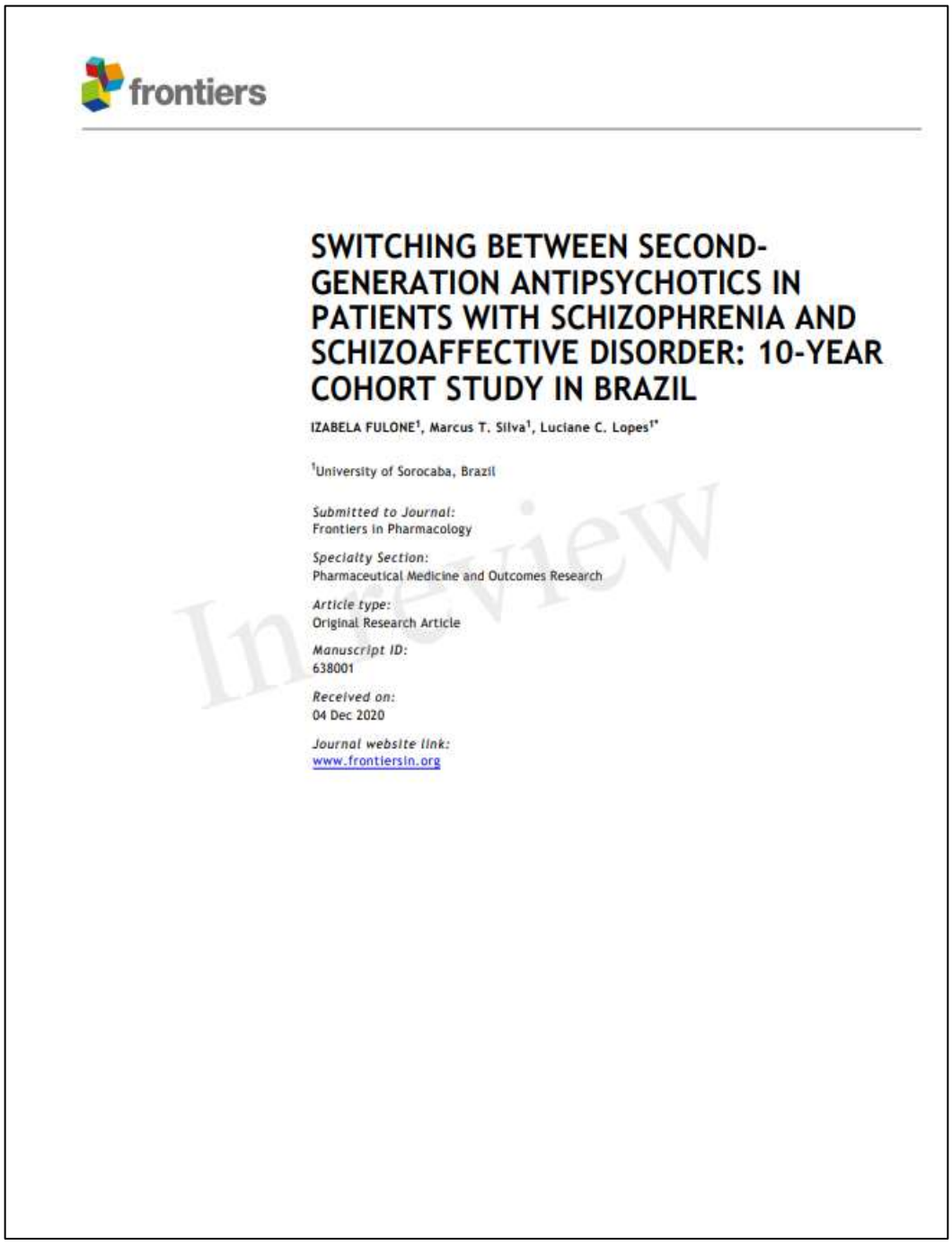
Manuscript ID:
575108

Received on:
22 Jun 2020

Frontiers website link:
www.frontiersin.org

In review

ANEXO E – COMPROVANTE DE SUBMISSÃO DO ARTIGO CIENTÍFICO 3



frontiers

SWITCHING BETWEEN SECOND-GENERATION ANTIPSYCHOTICS IN PATIENTS WITH SCHIZOPHRENIA AND SCHIZOAFFECTIVE DISORDER: 10-YEAR COHORT STUDY IN BRAZIL

IZABELA FULONE[1], Marcus T. Silva[1], Luciane C. Lopes[1*]

[1]University of Sorocaba, Brazil

Submitted to Journal:
Frontiers in Pharmacology

Specialty Section:
Pharmaceutical Medicine and Outcomes Research

Article type:
Original Research Article

Manuscript ID:
638001

Received on:
04 Dec 2020

Journal website link:
www.frontiersin.org

In review

ANEXO F – COMPROVANTE DE SUBMISSÃO DO ARTIGO CIENTÍFICO 4

BMC Psychiatry

Gender differences in the use of atypical antipsychotics in early-onset schizophrenia: a nationwide population based study in Brazil

--Manuscript Draft--

Manuscript Number:	BPSY-D-20-01406	
Full Title:	Gender differences in the use of atypical antipsychotics in early-onset schizophrenia: a nationwide population based study in Brazil	
Article Type:	Research article	
Section/Category:	Psychotic disorders	
Funding Information:	Fundação de Amparo à Pesquisa do Estado de São Paulo (2017/20668-7)	MSc Izabela Fulone
Abstract:	Introduction: The use of atypical antipsychotics for the treatment of schizophrenia and other mental disorders in populations under 18 years of age is increasing worldwide. Little is known about treatment patterns and the influence of gender differences, which may be a predictor of clinical outcomes. Objective: We aimed to investigate gender differences in the use of atypical antipsychotics in patients with early-onset schizophrenia (EOS) assisted by the public health system in Brazil. Methods: We conducted a cross-sectional study of outpatients with EOS aged 10 to 17 years who received at least one provision of atypical antipsychotics (clozapine, olanzapine, risperidone, quetiapine or ziprasidone) from a large Brazilian pharmaceutical assistance programme. Data were retrieved from a nationwide administrative database from 2008 - 2017. Results: Of the 49,943 patients with EOS, 63.5% were males, and the mean age was 13.6 years old. The patients were using risperidone (62.5%), olanzapine (19.6%), quetiapine (12.4%), ziprasidone (3.3%) and clozapine (2.2%). We found gender differences, especially in the 13-17 year age group (65.1% for males vs. 34.9% for females, $p<0.001$), in the use of risperidone (72.1% for males vs. 27.9% for females, $p<0.001$) and olanzapine (66.5% for males vs. 33.5% for females, $p<0.001$). Only in the 13 to 17 years age group were the prescribed doses of olanzapine ($p=0.012$) and quetiapine ($p=0.041$) slightly higher for males than for females. Conclusion: Our findings showed gender differences among patients diagnosed with EOS and who received atypical antipsychotics. More attention should be devoted to gender differences in research and clinical practice.	
Corresponding Author:	Luciane Cruz Lopes, Ph.D University of Sorocaba Sorocaba, São Paulo BRAZIL	
Corresponding Author E-Mail:	luslopesbr@gmail.com	
Corresponding Author Secondary Information:		
Corresponding Author's Institution:	University of Sorocaba	
Corresponding Author's Secondary Institution:		
First Author:	Izabela Fulone	
First Author Secondary Information:		
Order of Authors:	Izabela Fulone	
	Marcus Tolentino Silva	
	Luciane Cruz Lopes, PhD	
Order of Authors Secondary Information:		
Opposed Reviewers:		
Additional Information:		

Powered by Editorial Manager® and ProduXion Manager® from Aries Systems Corporation

ANEXO G – COMPROVANTE DE SUBMISSÃO DO ARTIGO CIENTÍFICO 5

MENU

terra

Conheça nossos serviços
Atendimento ao cliente

Entrada 1494
Rascunhos
Enviadas
Spam
Lixeira
Limpeza automática

VOLTAR | RESPONDER | RESPONDER A TODOS | ENCAMINHAR | É SPAM | REPORTAR FRAUDE | EXCLUIR | MOVER | MAIS

Recebimento de artigo - revista einstein

De: <revista@einstein.br> Adicionar contato Bloquear contato

Para: <mbfulone@terra.com.br>

Enviado em: Qua 23/12/20 18:16 Recebido em: Qua 23/12/20 18:17

São Paulo, 23 de dezembro de 2020

Ilmo(a). Sr(a). IZABELA FULONE

Confirmamos a agradecemos o recebimento de seu artigo PERFIL DE UTILIZAÇÃO DE ANTIPSICÓTICOS DE SEGUNDA GERAÇÃO EM PACIENTES COM ESQUIZOFRENIA ATENDIDOS NO SISTEMA UNICO DE SAUDE que foi protocolado sob o número AO-6407, para a seção Artigo Original. Esse número deverá ser utilizado para obter qualquer informação sobre a sua submissão.

Informamos ainda que será feita completa revisão por pares de seu manuscrito e que V.S* será notificado de nossas decisões.

Para acompanhamento de seu artigo acesse o sistema através do endereço eletrônico: http://apps.einstein.br/revista/index2.asp
Para se autenticar deverá digitar seu e-mail e senha.

Gratos pela sua colaboração, dispomo-nos.

Atenciosamente.

Prof. Dr. Sidney Glina
Editor Responsável