The brief needs assessment and professional practice gaps provided herein were independently developed by Lundbeck and are not intended to be exhaustive or directive.

Treatment Resistant Schizophrenia (TRS) Needs Assessment

Overview

Schizophrenia is a heterogeneous, progressive neurodevelopmental brain disease afflicting approximately 2.4 million adult Americans or about 1% of the world's population (Croxtall, 2011; Patel 2011). This disease is characterized by positive (i.e., hallucinations, delusions, disorganized speech), negative (i.e., blunted affect, avolition), and cognitive symptoms (i.e., poor executive functioning, trouble focusing, working memory impairment), with prognosis worsening with duration of untreated psychosis. (APA DSM-5, 2013; Patel, 2014; Lieberman, 2001; Shim, 2009). The confluence of varied genetic and environmental factors is thought to underlie the neural abnormalities observed in schizophrenia. These abnormalities include disruptions in brain structure and neural chemistry (Elkis, 2016).

Pharmacological treatment of schizophrenia includes to atypical and typical antipsychotic medications, which elicit a therapeutic response by acting as antagonists or partial agonists of dopamine D_2 receptors in the brain (APA Treatment Guidelines; Bruijnzeel, 2014; Stroup, 2016). Second-generation antipsychotics (SGAs) often act on other neurotransmitter systems as well. Despite the current armamentarium, approximately one-third of patients with schizophrenia do not respond to treatment with antipsychotics that preferentially target dopamine D_2 receptors (Stroup, 2016). Without an adequate response to antipsychotic treatment, patients are unlikely to benefit fully from other interventions designed to reduce the disease burden and facilitate social inclusion, such as psychosocial interventions, rehabilitation programmes, and social and community support (Tandon, 2006).

According to treatment guidelines, patients whose target schizophrenia symptoms have not responded to **two or more** antipsychotic treatments, at adequate dose and duration, meet the diagnostic criteria for treatment-resistant schizophrenia (TRS) (Hasan, 2012; Lehman, 2010; Howes, 2017).

No known psychopathology of schizophrenia predicts TRS (Shim, 2009). Risk factors for TRS differ from treatment-responsive schizophrenia and include younger age at first diagnosis (<20 years), rural living, previous suicide attempts and inpatient status at the onset of psychosis (Lally, 2016; Lieberman, 1999; Robinson, 1999). There are various biological hypotheses for TRS, including, but not limited to, dopamine-supersensitive type schizophrenia and normodopaminergic schizophrenia (Oda, 2015; Suzuki, 2015; Howes, 2014; Demjaha, 2012; Abi-Dargham, 2000).

Clinical Management of TRS

Other than clozapine, the only medication currently FDA-approved for TRS, limited options are available for patients with severe and significant residual symptoms after antipsychotic monotherapy has been optimized, and none has proven benefits (Lehman, 2004). Evidence-based national and international guidelines recommend clozapine for TRS after two AP trials (Lehman, 2004; Hasan, 2012). Although guidelines recommend starting clozapine after two treatment failures, its introduction is often delayed (Olfson, 2016; Howes, 2012). Not all patients with TRS respond to clozapine, and its use is limited by side effects and the need for regular blood testing (Clozaril PI, 2016; US FDA, 2016; Gee, 2014).

Switching antipsychotic medication has been employed as a treatment strategy for TRS. However, studies show that the superiority of switching strategies is low (Dold, 2014; Nyhuis, 2010). Combination therapy regimens have been used as well. However, these have not demonstrated robust efficacy and may increase the risk of metabolic side effects (Langan, 2010; Dold, 2014). Furthermore, there is insufficient evidence to recommend combination therapies, and current treatment guidelines recommend the use of antipsychotic monotherapies (Dold, 2014; Lehman, 2004; Hasan, 2012). Dose augmentation is another treatment strategy, but among several randomized clinical studies, no superiority of high-dose medication compared with the standard dose was shown for the majority of patients. High-dose antipsychotic treatment is not recommended as a general treatment option for TRS (Dold, 2014).

Burden of TRS

The social and economic burden of TRS can be addressed as a decrease in quality of life of both the patients and their family members, the presence of disease- and treatment-associated adverse effects, stigma, high medical costs, increasing rates of serious comorbidities, and increasing suicide risks (Kennedy, 2014). Mean quality of life of a TRS patient is considered to be 20% lower than in a treatment-responsive patient (Kennedy, 2014). An average of 64.5% of patients had perceived stigma, 55.9% had experienced stigma, and 49.2% reported isolation from the society (Baldwin & Marcus, 2006). Not only does TRS have high social and economic costs, unfavorable long-term outcomes are associated with the duration of insufficiently treated or untreated psychosis. (Wimberley, 2016). Patients with TRS, who show no or negligible signs of improvement with treatment, sustain longer hospital stays than expected and also have poor prognosis (Mouchlianitis, McCutcheon, & Howes, 2016). While costs for patients with schizophrenia are estimated between $15,500–$22,300 annually, the cost is 3- to 11-fold higher for patients with TRS. In the US direct medical costs associated with TRS are conservatively estimated at over $34 billion (Kennedy, 2014).

Professional Practice Gaps

- Psychiatrists and other mental healthcare professionals need to have an increased awareness of treatment-resistant schizophrenia (TRS) in order to recognize and effectively identify and treat patients with TRS.

- Psychiatrists and other mental healthcare professionals will benefit from education on the distinct pathophysiology and neurobiology of TRS in order to improve outcomes in patients with TRS and minimize the risk of inadequate treatment.

- Psychiatrists and other mental healthcare professionals who treat patients with TRS will benefit from an evidence-based education that reinforces clinical decision-making and evidence-based treatment strategies.

References

Abi-Dargham A, et al. Increased baseline occupancy of D2 receptors by dopamine in schizophrenia. *Proc Natl Acad Sci* USA 2000;97:8104–9.

APA. Diagnostic and statistical manual of mental disorders. 5th ed. 2013; Washington, DC.

Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. *Am J Psychiatry.* 2004;161(2 Suppl):1-56.

Baldwin ML, Marcus SC. Perceived and measured stigma among workers with serious mental illness. *Psychiatr Serv*. 2006 Mar;57(3):388-92.

Bruijnzeel D, et al. Antipsychotic treatment of schizophrenia: an update. *Asian J Psychiatr* .2014;11:3–7.

Clozaril®. Summary of product characteristics, 2016

Croxtall JD. Aripiprazole: A Review of its Use in the Management of Schizophrenia. *CNS Drugs.* 2011;24(12);1-27.

Demjaha A, et al. Dopamine synthesis capacity in patients with treatment-resistant schizophrenia. *Am J Psychiatry*.2012;169:1203–10.

Dold M, Leucht S. Pharmacotherapy of treatment-resistant schizophrenia: a clinical perspective. *Evid Based Ment Health*.2014;17:33–7.

Gee S, et al. Practitioner attitudes to clozapine initiation. *Acta Psychiatr Scand*.2014;130:16–24.

Hasan A, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. *World J Biol Psychiatry*.2012;13:318–78

Howes OD, et al. Treatment-Resistant Schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group Consensus Guidelines on Diagnosis and Terminology. *Am J Psychiatry*. 2017 Mar 1;174(3):216-229

Howes OD, et al. Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry*.2012, 201:481–5

Howes OD, Kapur S. A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic). *Br J Psychiatry*. 2014 Jul;205(1):1-3.

Kennedy JL, Altar CA, et al. The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol*. 2014 Mar;29(2):63-76.

Lally J, et al. Treatment-resistant schizophrenia: current insights on the pharmacogenomics of antipsychotics. *Pharmgenomics Pers Med*. 2016; 9: 117–129.

Langan J, Shajahan P. Antipsychotic polypharmacy: Review of mechanisms, mortality and management. *The Psychiatrist*.2010;34:58–62.

Lieberman JA, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biol Psychiatry*.2001;50:884–97.

Lieberman JA. Pathophysiologic mechanisms in the pathogenesis and clinical course of schizophrenia. J *Clin Psychiatry.* 1999;60(Suppl)12:9–12.

Mouchlianitis E, McCutcheon R, Howes OD. Brain-imaging studies of treatment-resistant schizophrenia: a systematic review. *Lancet Psychiatry*. 2016 May;3(5):451-63

Nyhuis AW, et al. Predictors of switching antipsychotic medications in the treatment of schizophrenia. *BMC Psychiatry*.2010;10:75.

Oda Y, et al.Alterations of Dopamine D2 Receptors and Related Receptor-Interacting Proteins in Schizophrenia: The Pivotal Position of Dopamine Supersensitivity Psychosis in Treatment-Resistant Schizophrenia. *Int J Mol Sci*.2015;16;30144–63.

Olfson M, et al. Clozapine for Schizophrenia: State Variation in Evidence-Based Practice. *Psychiatr Serv*. 2016:67:152

Patel KR, Cherian J, Gohil K, Atkinson D. Schizophrenia: overview and treatment options. *Pharmacy and Therapeutics*. 2014 Sep;39(9):638-45

Robinson DG, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry*.1999;156:544–9.

Shim, S. S. 2009 Aug 17. Treatment-Resistant Schizophrenia. Retrieved from Psychiatric Times.com: www.psychiatrictimes.com/schizophrenia/treatment-resistant-schizophrenia/page/0/1

Stroup TS, et al. Comparative Effectiveness of Clozapine and Standard Antipsychotic Treatment in Adults With Schizophrenia. *Am J Psychiatry*.2016;173:166–73.

Suzuki,T et al. Dopamine supersensitivity psychosis as a pivotal factor in treatment-resistant schizophrenia. *Psychiatry Res*. 2015 Jun 30;227(2-3):278-82.

Tandon R, et al. Strategies for maximizing clinical effectiveness in the treatment of schizophrenia. J *Psychiatr Pract*. 2006;12:348–63.

US Food and Drug Administration (FDA). Clozapine drug safety communication. Last accessed December 2016.

Wimberley T, et al. Predictors of treatment resistance in patients with schizophrenia: a population-based cohort study. *Lancet Psychiatry*. 2016 Apr;3(4):358-66.