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 D2 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 D2 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

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