Asian Journal of Psychiatry 11 (2014) 3–7

Contents lists available at ScienceDirect

Asian Journal of Psychiatry

journal homepage: www.elsevier.com/locate/ajp

Review

Antipsychotic treatment of schizophrenia: An update

Dawn Bruijnzeel, Uma Suryadevara, Rajiv Tandon *

Department of Psychiatry, University of Florida College of Medicine, 1149 Newell Drive, L4-100, Gainesville, FL 32611, USA

ARTICLE INFO

Article history:
Received 7 August 2014
Accepted 10 August 2014

Keywords:
Schizophrenia
Treatment
Antipsychotic
Review
Effectiveness
Guideline

ABSTRACT

The primary objectives in the treatment of schizophrenia are to reduce the frequency and severity of psychotic exacerbation, ameliorate a broad range of symptoms, and improve functional capacity and quality of life. Treatment includes pharmacotherapy and a range of psychosocial interventions. Antipsychotics are the cornerstone of pharmacological treatment for schizophrenia. The sixty-five antipsychotics available in the world are classified into two major groups: first-generation (conventional) agents (FGAs) and second-generation (atypical) agents (SGAs). Whereas clozapine is found to be more efficacious than other agents among otherwise treatment-refractory schizophrenia patients, other differences in efficacy between antipsychotic agents are minor. There are, however, pronounced differences in adverse effect profiles among the 65 antipsychotic medications. Although the 14 SGAs differ "on average" from the 51 FGAs in terms of being associated with a lower risk of EPS and greater risk of metabolic side-effects, substantial variation within the two classes with regard to both risks and other relevant clinical properties undermines the categorical distinction between SGAs and FGAs. Choice of antipsychotic medication should be based on prior treatment response, individual preference, medical history and individual patient vulnerabilities. An individualized treatment approach with ongoing risk–benefit monitoring and collaborative decision-making is outlined. Even as rapid neuroscience advances promise revolutionary improvements in the future, a thoughtful and disciplined approach can provide enhanced outcomes for all schizophrenia patients today.

Contents

1. Introduction

Schizophrenia is a chronic remitting and relapsing psychotic disorder with significant impairments in social and vocational functioning, multiple psychiatric and medical comorbidities, and increased mortality (Tandon et al., 2008a, 2009). There are multiple illness dimensions that are variably responsive to

* Corresponding author. Tel.: +1 352 294 0400; fax: +1 352 379 2627.
E-mail address: tandon@ufl.edu (R. Tandon).

http://dx.doi.org/10.1016/j.ajp.2014.08.002
1876-2018/

currently available treatments which include medications, psychological therapies, and social supports (Tandon et al., 2008b, 2013a,b). Since the introduction of chlorpromazine, the first antipsychotic, into clinical practice 60 years ago, antipsychotic medications have become the cornerstone in the pharmacotherapy of schizophrenia. This article provides a broad overview of available antipsychotics and guidance regarding their utilization in the treatment of schizophrenia.

2. Antipsychotic agents: pharmacology

There are 65 antipsychotic medications utilized across the world and 15–40 of these agents are available in any country. They are classified into groups of first- and second-generation antipsychotics (FGAs and SGAs, respectively), with the one pharmacological property shared by all currently available antipsychotic agents being their ability to block the dopamine D-2 receptor (Creese et al., 1976; Johnstone et al., 1978; Kapur and Remington, 2001). Aripiprazole, the only antipsychotic which is not a D-2 antagonist, is a partial agonist with low intrinsic activity at the D-2 receptor and therefore behaves as an antagonist in the mesolimbic dopamine system. Even with reference to dopamine D-2 antagonism (or partial agonism in the case of aripiprazole), antipsychotic medications differ in their binding affinity to the receptor. Antipsychotic medications have a range of other pharmacological properties with significant differences among available agents which, in turn, substantially explains differences in their side-effect profiles. Antipsychotic agents also differ with reference to a range of pharmacokinetic attributes and while all 65 are available in an oral formulation, 13 are available as short-acting injectable preparations and 11 as long-acting injectable preparations.

3. Efficacy

Schizophrenia is characterized by positive symptoms, disorganization, negative symptoms, cognitive deficits, mood and motor symptoms, with the types and severity of symptoms differing among patients and over the course of the illness (Heckers et al., 2010; Tandon and Carpenter, 2012; Tandon and Maj, 2008; Tapp et al., 2001). Both FGAs and SGAs are effective in reducing positive and disorganization symptoms, but are only minimally effective for negative and cognitive symptoms which contribute significantly to the disability associated with schizophrenia. Antipsychotics have been consistently found to be superior to placebo in reducing risk of relapse in schizophrenia (Gilbert et al., 1995; Leucht et al., 2012), with no consistent differences amongst the different antipsychotic agents in this regard. While virtually all FGAs were introduced into clinical practice between 1952 and 1976, clozapine was the only SGA developed during that time. Since 1990, thirteen additional SGAs were introduced into clinical practice which were all initially believed to be more efficacious and tolerable than FGAs. However, results of large-scale studies, such as the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, which compared one FGA (perphenazine) and four SGAs (olanzapine, quetiapine, risperidone, and ziprasidone), indicated that the SGAs may be no more effective than the FGAs and also may not be associated with better cognitive or social outcomes (Keefe et al., 2007; Lieberman et al., 2005; Swartz et al., 2007). The European First Episode Schizophrenia Trial, which compared open-label treatment with haloperidol, amisulpride, olanzapine, quetiapine, or ziprasidone in first-episode schizophrenia, also suggested the absence of significant benefits for SGAs over FGAs (Davidson et al., 2009; Kahn et al., 2008).

A meta-analysis of haloperidol-controlled trials indicated that only some SGAs (notably clozapine, olanzapine, amisulpride, and risperidone) were more efficacious than haloperidol (Leucht et al., 2009a). Although this observation can be partly explained by differences in the haloperidol dose used in the different trials (Geddes et al., 2000; Hugenholtz et al., 2006; Tandon and Nasrallah, 2006), the modest differential efficacy cannot be dismissed as a mere methodological artifact (Leucht et al., 2013). In contrast, no major differences in efficacy among various antipsychotics have been observed in meta-analyses of placebo-controlled studies, with haloperidol found to have efficacy similar to the SGAs (Tandon and Jibson, 2005; Leucht et al., 2009b). Though limited, comparisons of SGAs with low- and mid-potency FGAs and comparisons among the FGAs suggest no consistent differences in efficacy, except for clozapine's superiority in treatment-refractory schizophrenia (Kane et al., 1988). Finally, direct comparisons between various SGAs reveal inconsistent differences in efficacy, except for an advantage for clozapine in treatment-refractory schizophrenia (McEvoy et al., 2006; Leucht et al., 2009c; Lewis et al., 2006). Comparative studies in the early stages of schizophrenia have also found no significant differences in efficacy among antipsychotics (Derks et al., 2010; Salimi et al., 2009).

All available antipsychotics have robust efficacy for positive symptoms and disorganization, with no consistent differences found in efficacy for these domains. Response over the first 2–4 weeks of antipsychotic therapy is highly predictive of long-term response (Kinon et al., 2010). The maximum effect, however, may not be achieved for several months, and trajectories of response vary considerably across patients. Responsiveness to antipsychotics also varies as a function of stage of illness, with first-episode patients responding faster and at a higher rate than those at later stages of the illness (Emsley et al., 2006). Antipsychotics are less consistently effective in reducing negative symptoms and much of their effect on negative symptoms may be associated with reduction in positive symptoms. While antipsychotics ameliorate negative symptoms linked with positive symptoms, they can worsen negative symptoms associated with EPS (Tandon et al., 2000). Antipsychotic agents have no demonstrable efficacy against primary enduring (''deficit'') negative symptoms. Similarly, antipsychotics can ameliorate depressive symptoms in conjunction with producing improvement in positive symptoms, but can also cause ''neuroleptic dysphoria'' associated with EPS (Voruganti and Awad, 2004). Although antipsychotics can improve attention in patients with schizophrenia, findings concerning their effects on other cognitive impairments are inconsistent and may include worsening of cognition. No consistent differences have been found among antipsychotics in effects on neurocognitive dysfunction, with net impact determined by the agent's beneficial effects on attention versus deleterious effects due to EPS and anticholinergic activity of the antipsychotic and of anticholinergic agents used to treat EPS (Hill et al., 2010; Tandon et al., 2010). Consequently, the net effect of an antipsychotic on negative symptoms is generally determined by the extent to which it reduces negative symptoms associated with positive symptoms and triggers negative symptoms related to EPS; the same applies for antipsychotic effects on the domains of depression and cognition. Antipsychotic medications substantially decrease likelihood of relapse in schizophrenia, without any consistent differences among agents (Leucht et al., 2012). Since medication nonadherence is common in schizophrenia, long-acting injectable antipsychotics may have an advantage over oral treatment in reducing relapse rates (Nasrallah, 2007).

4. Safety and tolerability

Antipsychotic medications cause a range of neurological, metabolic, cardiovascular, gastrointestinal, hematological,