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Review

Implications of epigenetic modulation for novel treatment approaches in patients with schizophrenia

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ABSTRACT

Schizophrenia is a heterogeneous and complex mental disorder with high rates of disability, non-recovery, and relapse. The primary pharmacological treatments for schizophrenia are antipsychotics. Notwithstanding the efficacy of antipsychotics in ameliorating positive symptoms and reducing relapse rates, cognitive deficits and negative symptoms are not sufficiently treated with available pharmaceutical agents. Moreover, schizophrenia is associated with consistent, replicable, and clinically significant deficits in cognition. The importance of cognitive deficits in schizophrenia is emphasized by reports indicating that the severity of cognitive deficits is predictive of treatment compliance, adherence, and risk of relapse among first-episode individuals. Taken together, this review highlights epigenetic modulations involving histone deacetylase (HDAC) inhibitors as a potential avenue for novel treatment toward improvements in cognition and functional outcomes in patients with schizophrenia. The combination of epigenetic modulation with pharmacological interventions that engage multiple disparate physiological systems implicated in schizophrenia are discussed, and may represent a more effective strategy in ameliorating cognitive deficits and mitigating symptoms for improved functionality.

1. Introduction

Schizophrenia is a complex, chronic, and heterogeneous psychiatric disorder with high rates of disability, non-recovery, and relapse (Galletly, 2009). Moreover, schizophrenia is associated with consistent, replicable, and clinically significant deficits in cognition (Davidson et al., 2009; Sharma et al., 2006; Bowie et al., 2006). Cognitive deficits represent a core feature of schizophrenia with the aggregate estimate effect size reported as mild-to-moderate (i.e., 1.5–2.5 standard deviations below population norms), affecting approximately 75%–85% of individuals (Gray et al., 2007; Keefe et al., 2007; Bilder et al., 2000; Gold et al., 1999; Heinrichs et al., 1998). Pronounced deficits in cognition are frequently reported to precede the onset of positive symptoms and continue to persist despite successful treatment of positive symptoms (Gray et al., 2007).

The primary pharmacological treatments for schizophrenia are antipsychotics. Notwithstanding the efficacy of antipsychotics in ameliorating positive symptoms and reducing relapse rates, cognitive deficits and negative symptoms are not sufficiently treated with available pharmaceutical agents (Buchanan et al., 2007; Burdick et al., 2011). The importance of cognitive deficits in schizophrenia is emphasized by reports indicating that the severity of cognitive deficits is predictive of treatment compliance, adherence, and risk of relapse among first-episode individuals (Gray et al., 2007; Chen et al., 2005; Prouteau et al., 2005). Emerging evidence suggests that cognitive deficits and negative symptoms (e.g., blunted affect, social withdrawal, amotivation) have the greatest impact on functional outcomes (e.g., quality of life, psychosocial, occupational) (Davidson et al., 2009; Bowie et al., 2006; Buchanan et al., 2007; Mohamed et al., 2008; Kraus et al., 2007; Kurtz et al., 2013; Lin et al., 2013). More specifically, negative symptoms have been reported to mediate the influence of

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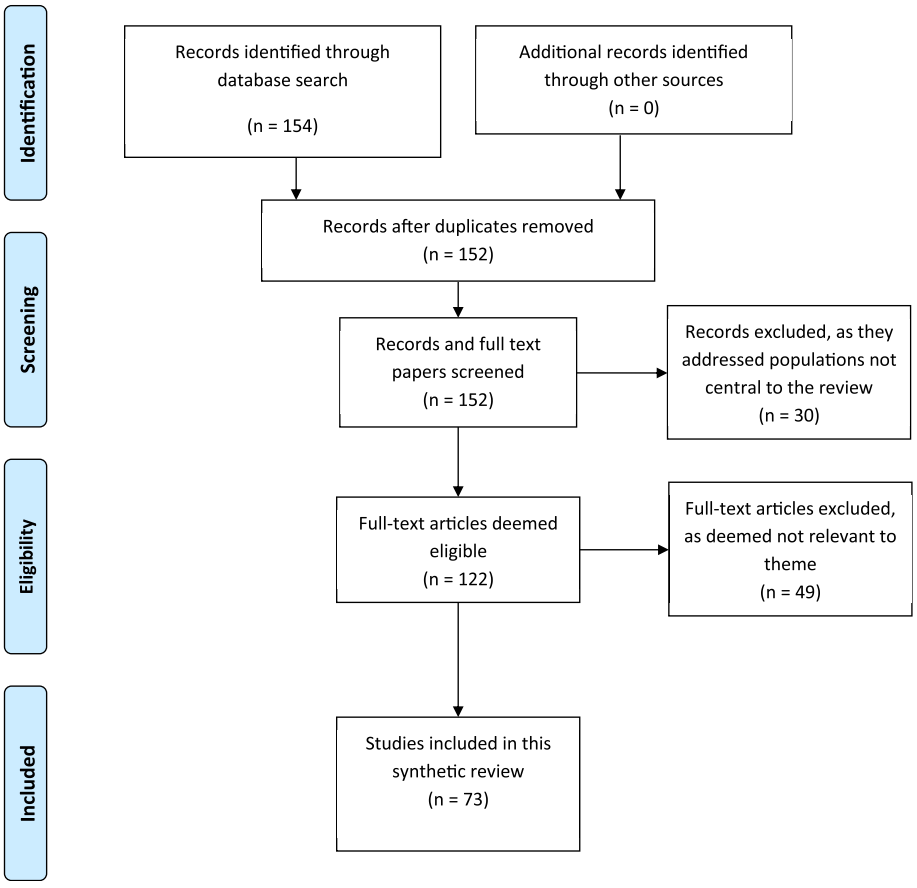

Fig. 1. PRISMA diagram for review eligibility and inclusion.

cognition on functional outcomes in schizophrenia (Davidson et al., 2009; Bowie et al., 2006; Buchanan et al., 2007; Mohamed et al., 2008; Kraus et al., 2007; Kurtz et al., 2013; Lin et al., 2013; Ventura et al., 2009). However, results have been mixed with separate lines of evidence suggesting that indices of cognitive deficits are superior predictors of functional outcome when compared to any other symptom domain (Gray et al., 2007; Mohamed et al., 2008; Lin et al., 2013; Lipkovich et al., 2009; Rodriguez-Sanchez et al., 2007; Silverstein and 2008; Milev et al., 2005).

The hazards posed by cognitive deficits among individuals with schizophrenia represented a reasonable basis for the discovery of novel cognitive enhancing pharmacological agents (Mohamed et al., 2008; Buchanan et al., 2005; Green, 2007; Marder and 2011). During the past decade, studies evaluating the effects of second generation antipsychotics – distinguished by their reduced extrapyramidal side effect profiles – have reported beneficial effects on cognitive function when compared to first generation antipsychotics (Harvey et al., 2001). However, the difference between first generation and second-generation antipsychotics are modest with a standard deviation in the range of 0.2–0.4 (Keefe et al., 2007; Green, 2007). Moreover, the reported benefits of second generation antipsychotics on cognitive function have been disputed and remain controversial (Keefe et al., 2013; Keefe and Harvey, 2012). For example, in a study investigating the efficacy of first generation vs. second generation antipsychotics on cognitive function in a sample of 817 individuals from the Clinical and Antipsychotic Trials of Intervention Effectiveness (CATIE), subjects were randomized to either a first generation (i.e., perphenazine) or second generation antipsychotic (i.e., olanzapine, quetiapine, risperidone, and ziprasidone) for two months of treatment (Keefe et al., 2007; Keefe and Harvey, 2012). Results demonstrated that all groups experienced minor improvements in cognitive function over the course of the study; however, no significant differences in cognition were noted between the two generations of antipsychotics (Keefe et al., 2007; Keefe and Harvey, 2012). Notwithstanding the ongoing changes and improvements in sample size and methodology, no cognitive enhancing agents have emerged as clinically significant among individuals with schizophrenia (Galletly 2009; Lee et al., 2007; Goff et al., 2008).

Alternative avenues for further drug development in this area are warranted. Epigenetic modifications mediated by molecular mechanisms may be a promising new target for improving both cognitive deficits and symptom severity to improve functional outcome in schizophrenia. This proposal is based on the working assumption that epigenetic mechanisms can be specifically targeted and manipulated by pharmacological intervention(s) (Kurita et al., 2012; Citrome et al., 2004; Kelly et al., 2006; Suzuki et al., 2009; Loscher and 1999; Gurvich et al., 2004; Graff et al., 2009). For example, histone deacetylase inhibitors have been demonstrated to facilitate learning and memory, alter synaptic plasticity, and impact affect regulation as well as antipsychotic efficacy (Kurita et al., 2012; Morris et al., 2013, 2010; Hyman 2012; Grissom et al., 2009; Chuang et al., 2009; Guan et al., 2009; Graff and Tsai, 2013).

This review highlights epigenetic modulations involving histone deacetylase (HDAC) inhibitors as a potential avenue for novel treatment toward improvements in cognition and functional outcomes in patients with schizophrenia. The overarching aim is to describe how the combination of epigenetic modulation with