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Mini Review

Treating Schizophrenia Thinking beyond the Choice of Antipsychotic

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ABSTRACT

The treatment of schizophrenia has evolved over the past half century primarily in the context of antipsychotic drug development. Although there has been significant progress resulting in the availability and use of numerous medications, these reflect three basic classes of medications (conventional (typical), atypical and dopamine partial agonist antipsychotics) all of which, despite working by varying mechanisms of actions, act principally on dopamine systems. Many of the second-generation (atypical and dopamine partial agonist) antipsychotics are believed to offer advantages over first-generation agents in the treatment for schizophrenia. However, the pharmacological properties that confer the different therapeutic effects of the new generation of antipsychotic drugs have remained elusive, and certain side effects can still impact patient health and quality of life. Moreover, the efficacy of antipsychotic drugs is limited prompting the clinical use of adjunctive pharmacy to augment the effects of treatment. In addition, the search for novel and non-dopaminergic antipsychotic drugs has not been successful to date, though numerous development strategies continue to be pursued, guided by various pathophysiologic hypotheses. This article provides a brief review and critique of the current therapeutic armamentarium for treating schizophrenia and drug development strategies and theories of mechanisms of action of antipsychotics, and focuses on novel targets for therapeutic agents for future drug development.

Keywords: Schizophrenia; Antipsychotic drugs; Psychosis; Hyperprolactinaemia

INTRODUCTION

English and Castle suggest an updated Royal Australian and New Zealand College of Psychiatrists (RANZCP) Clinical Practice Guidelines (CPG) for schizophrenia and related disorders should be informed "most explicitly" by the side-effect profile and risk amelioration potential of available antipsychotics. Given the (relative) comparable efficacy of most available antipsychotics, this approach is not unreasonable and would be in line with several other contemporary international guidelines. In addition, it would be prudent to incorporate the (appropriately informed) views and preferences of the patient in a shared decision-making process. The authors highlight three key side effects of antipsychotics deemed most physically significant:

Tardive dyskinesia (TD).

Metabolic syndrome (MetS).

Hyperprolactinaemia.

When it comes to psychotropics, there are arguably no such thing as "side" effects – there are just "effects". Effects may be interpreted as beneficial or adverse depending on the person, time and circumstances. For example, sedation from olanzapine may be considered beneficial in a person tormented by psychosis and/or insomnia, but adverse in a person attending a 9 am job interview. Suffice to say, the three listed "side" effects are universally considered adverse (perhaps with the rare exception of a post-partum woman with inadequate milk supply prescribed a "galactagogue" to induce hyperprolactinaemia). The word "side" implies there is a "central" effect, but psychotropic drugs have wide-ranging effects on multiple receptors across multiple brain regions – beneficial effects are tied together with other, more global effects. One such example is the indiscriminate blockade of D2 across multiple brain pathways by antipsychotics. In the mesolimbic pathway, acutely, it is hypothesised this results

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in diminution of positive psychotic symptoms. In the nigrostriatal pathway, chronically, it is hypothesised this may be a cause of TD.

LITERATURE REVIEW

TD is a chronic, potentially disabling motor syndrome characterised by persistent, repetitive abnormal involuntary movements. As English and Castle point out, upregulation of the D2-receptor in response to D2 blockade is implicated in the evolution of TD. This, along with an increase in the proportion of D2-receptors in the "high affinity" state for dopamine, is considered a neuroadaptive homeostatic response to an altered neurophysiological environment-a process described as "dopamine supersensitisation" [1]. Some evidence suggests partial D2-agonists may not induce the same response. In line with this, the authors reference a recent meta-analysis where the partial D2-agonist aripiprazole carried the lowest risk of TD and reasonably speculated about the newer D2/D3 partial agonists (brexpiprazole and caripirazine) carrying a similarly lower risk. In sum, the authors endorse an aetiological model for TD that involves upregulation of D2-receptors consequent to chronic D2-receptor antagonism and imply the problem is significant enough to warrant specifically listing agents that may reduce this risk. TD is considered (primarily) the manifestation of nigrostriatal supersensitisation given antipsychotics indiscriminately block D2-receptors across the brain, what about the consequences of supersensitisation elsewhere?

Supersensitivity Psychosis (SP) refers to psychosis hypothetically precipitated by stimulation of a "supersensitised" mesolimbic post-synaptic membrane. SP may be considered a etiologically analogous to TD, albeit in a different brain pathway. The clinical result is a paradoxically increased risk of psychotic relapse in those taking long-term (>3 months) antipsychotics following dose reduction, switch or cessation; or "breakthrough psychosis" in those on continuous treatment. It follows that efforts to minimise the risk of TD should also minimise the risk of SP-English and Castle's nod to the partial agonists here appears apt-choice of antipsychotic based on pharmacodynamic profile is important. Dose, frequency and duration of exposure, however, are also all variables that affect the risk of developing TD and SP-these go unmentioned. If we accept the putative pathophysiology of TD then we should seriously consider the same for SP and therefore reappraise those factors deemed material to the risk of both. By inducing supersensitisation, the current RANZCP recommendations for continuous antipsychotic treatment for all cases of FEP for a minimum of 2-5 years at "target doses" may actually be harmful.

Chouinard recently proposed guidelines for the prevention of both TD and SP – the choice of antipsychotic formed one of several recommendations [1]. Firstly, the guidelines highlight the role of prevention and detection (e.g. monitoring with validated scales, using lower risk agents at lower doses and, where clinically appropriate, increasing the interval between doses and/or discontinuing after a several-month taper). Secondly, they discuss the choice of antipsychotic (e.g. using SGAs associated with few/no movement disorders including low-dose partial D2-agonists before the development of TD/SP, and avoiding higher-risk drugs including most FGAs). Finally they suggest adding an adjunctive low-dose anticonvulsant (rationale provided). Though theoretically sensible, such recommendations have gained little traction in mainstream practice. However, emerging evidence supporting "minimal-medication" approaches may just change this.

A recent Australian study examined 90 patients with FEP deemed "low risk", randomised to antipsychotic or placebo (with intensive psychosocial intervention). At 6 months there was no difference in symptomatic or functional outcomes [2]. In the UK, Morrison et al. randomised 61 patients with FEP to either antipsychotic, psychological intervention or a combination. At 6 months, all three groups had improved significantly on the PANSS, with the highest proportion of "responders" in the psychological intervention-only group [3]. Two systematic reviews, involving 2,250 people with psychosis or schizophrenia, have compared "minimal medication" approaches (including psychosocial treatments) with antipsychotic treatment-as-usual (TAU). Compared to TAU, "minimal medication" approaches were at least as effective in attenuating symptoms and improving functioning with no increased risk of harms [4]. In response to pressure from consumer groups, some countries have created alternatives to antipsychotic-TAU-based services for psychosis. Since 2015, Norway has established 14 hospital units with "drug-free" treatment programs that include outpatient services. In the USA, a "Soteria House" operates in the state of Vermont [4]. Formal evaluations of these programs are pending, but anecdotal reports are favorable.

Expressing his concerns about the development of D2 super sensitivity consequent to continuous antipsychotic treatment, eminent schizophrenia researcher Robin Murray recently stated that 40% of those with FEP-in-remission should achieve good long-term outcomes with either no antipsychotic medication or very low doses [5]. Whilst there is no such thing as a neurochemical free lunch, we can always do better to minimise the bill [6].

DISCUSSION AND CONCLUSION

The choice of antipsychotic in the treatment of psychosis is critically important-English and Castle were right to promote deliberation on drugs that minimise the risk of TD, MetS and hyperprolactinaemia. But if we accept the putative pathophysiology of TD, we should also pay attention to that of SP and aim to minimize the risks of both – this involves careful consideration of not just the choice of drug but also the dose, frequency, and duration of treatment. Evidence is mounting in support of "minimal-medication" approaches to FEP that challenge the current RANZCP recommendations to treat all cases of FEP with continuous antipsychotics at "target" doses for 2-5 years. With the premise of "first do no harm", perhaps future RANZCP CPGs could reflect a paradigm shift away from a psychopharmacological one-size-fits-all approach to individualized treatment plans that allow for "minimal-medication" strategies where possible, and "antipsychotic-TAU" strategies where clinically indicated, or indeed preferred. This article provides a brief review and critique of the current

therapeutic armamentarium for treating schizophrenia and drug development strategies and theories of mechanisms of action of antipsychotics, and focuses on novel targets for therapeutic agents for future drug development.

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