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Prospects of schizophrenia Relapse pharmacotherapy research: bench or bedside?

Abbreviations: NME, new molecular entity; NCE, new chemical entity; QXR, quetiapin extended release

Editorial

Schizophrenia is a complex, multidimensional, heterogeneous mental disorder prevalent in approximately 1% of the world's population.[1,2] A global consensus is lacking in the diagnostic criteria and pathophysiology of schizophrenia mainly due to the heterogeneity in the array of its symptoms. Many hypotheses aimed at understanding the biology and treatments of schizophrenia implicate disruption of synaptic dopaminergic, glutamatergic and GABAergic neurotransmission and their receptors.[3,4] The course of schizophrenia is often progressive and is characterized with frequent relapses and thus, long-term control of the psychotic symptoms and reducing the relapse rate is an important therapy target to minimize socio-economic impact of the disorder.

In pharmacotherapy of schizophrenia, as a class, antipsychotic drugs have remained as mainstay since 1950s. Accumulating data of suboptimal outcomes and multiple adverse effects associated with therapy using the first-generation ("*conventional/typical*") antipsychotic drugs compelled adopting the classic route of bench research to explore New Molecular Entity [NME]/New Chemical Entity [NCE] with potential to be more effective and safe and lead to the development of multiple second-generation ("*atypical*") antipsychotic drugs. At present, although many second-generation antipsychotic drugs are available for prescription, few differences exist among them in their short-term efficacy.[5] Moreover, some comparative data analyses of efficacy and tolerability of antipsychotic drugs in schizophrenia appear to challenge the straightforward classification of antipsychotics into first-generation and second-generation categories.[6]

International therapy guidelines for schizophrenia identify relapse-prevention as a key objective, although criteria to define the relapse remains yet to be established.[7] Systematic review and meta-analyses of the "*bed-side*" data on relapse prevention suggest:

i. Continuous antipsychotic medication appears to be one of the most prominently reported factors to reduce the risk of relapse and should be a priority for psychiatrists.[7]

ii. Treatment selection needs to be individualized, considering patient and medication-related factors.

iii. Sufficiently large data sets are needed to allow the examination of the relative merits of individual second generation antipsychotic drugs and to guide an individualized and evidence-based maintenance treatment selection.[8]

The product development route for evolving relapse prevention regimens relied on developing antipsychotic drugs that are either extended release oral formulations, or parenteral formulations better suited for integration into rehabilitation programs. The formulations that have been developed include intranasal, transdermal patches,

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subcutaneous implants as well as long acting pumps.[9] An extended release oral formulation of the second-generation antipsychotics, Quetiapine (QXR) is available for prescription as a treatment of schizophrenia. In one study, relapse prevention efficacy of QXR was compared with lurasidone.[10] This study with rigorous design (double-blind paradigm, prespecified criteria for both relapse and non-inferiority analysis) compared a flexible dose of lurasidone (40–160mg/d) with QXR (200–800mg/d). The results from this 12months study suggests, long-term non-inferiority studies using an active comparator are feasible in patients with schizophrenia and such studies may provide clinical differentiation among antipsychotic drugs.

Inferences on effective relapse prevention pharmacotherapy paradigms in schizophrenia that are based on systematic review and metat-analyses are of limited generalizability, because of factors such as, studies included, scope of the key questions and inclusion criteria. Obviously, despite substantial research into the etiopathology and availability of multiple drugs, pharmacotherapy paradigms for schizophrenia relapse remain empirical. Nevertheless, several recent developments, with potentials for breakthrough are noteworthy:

a. In this era of increased understanding on the genetic basis of patient-specific eitopathology, schizophrenia genomics has identified >100 risk loci and emerging technology like genome editing hold promise for identifying novel drug targets.[11]

b. Drug repositioning using computer-based disease models and databases are not perfect. However, *in silico* technologies hold promise for antipsychotic drug selection prior to clinical testing.[12]

c. Emerging research on:

i. Electroceuticals target individual nerve fibers or specific brain circuits.[13]

ii. Deep brain stimulation methodologies provide insights into brain functions in psychiatric diseases.[14] Prostheses that can re-establish and sustain the structural and functional integrity of the brain circuits[15] is a new avenue of research.

These developments hold promise for a new era of individualized therapy of schizophrenia relapse. Clearly, we are at an exciting cross

road, with multiple potential paths for progress. Only future can reveal which of these path(s) would be beneficial for reaching the final target of individualized treatment.

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Conflict of interest

Author declares that there is no conflict of interest.

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