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EDITORIAL

Shortening Duration of Treatment Resistance: The Next Step in the Treatment of Schizophrenia

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The early psychosis movement was fuelled by the concept that early recognition and treatment of patients with psychosis could prevent long-term chronic impairment. Indeed, duration of untreated psychosis (DUP) predicts treatment response and early intervention services have since shown added value. However, considerable chronic impairment remains, with about 20%–30% of the patients with schizophrenia not responding to 2 different conventional antipsychotics in adequate doses and duration. In contrast to the research on DUP and early intervention in schizophrenia in general, far less research has systemically assessed the benefits of shortening the time between treatment onset and adequate treatment response. Yet timely recognition of treatment-resistant schizophrenia (TRS) could be vital since studies have indicated that a critical time window in which clozapine is most effective for TRS patients could exist. We believe that introducing the concept of Duration of Treatment Resistance (DTR) may help to investigate whether shortening of DTR by optimizing medication schedules can further prevent or mitigate long-term disability in patients with schizophrenia. In this editorial, we propose a definition of DTR and encourage the field to investigate the potential merits of this concept in future studies.

Key words: schizophrenia/treatment resistance/early intervention/clozapine remission

Viewpoint

The early psychosis movement was fuelled by the concept that earlier recognition and treatment of patients with schizophrenia could prevent long-term chronic impairment. Indeed, duration of untreated psychosis (DUP) predicts treatment response and early intervention services have since shown added value.[1,2]

However, considerable chronic impairment remains, with about 20%–30% of the patients with schizophrenia not responding to 2 different conventional antipsychotics in adequate doses during at least 6 weeks.[3,4] These patients are considered to have treatment-resistant schizophrenia (TRS), although resistance to conventional antipsychotics would be more apt, as about 50% of these patients do show a beneficial response to clozapine.[3,4]

Unfortunately, clozapine still remains underutilized in TRS. Initiation of clozapine is often started years after treatment onset, while patients go through unsuccessful trials of 4 or more antipsychotics.[2] In this period, substantial disability and damage to supporting networks of family and friends have often developed, increasing the probability that patients end up permanently institutionalized or homeless.

In contrast to the research on DUP and early intervention in schizophrenia, far less research has systemically assessed benefits of shortening the time between treatment onset and adequate treatment response. Yet timely recognition of TRS could be vital, since studies have indicated that a critical time window in which clozapine is most effective for this group of patients could exist.[5] Furthermore, in clozapine non-responders, electroconvulsive therapy may further improve remission rates.[4]

The identified clinical and demographic factors that are associated with treatment response (DUP, age at onset, negative symptoms[3]) are insufficient to predict treatment response in individual patients. Biomarkers are pursued to help early identification of potential

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TRS.[1,4] A promising predictor is striatal dopamine synthesis capacity, since this is increased in patients responding to conventional antipsychotics but not in TRS patients. Instead, a variety of studies recognize TRS as a subgroup, which might be characterized by more marked glutamate alterations.[4] Other research points at serotonin pathway dysfunction, inflammation, and oxidative stress.[4] More research is needed to determine which biomarker findings are robust and translatable to clinical practice.

As biomarkers will not be available for clinical practice in the foreseeable future, we believe that introducing the concept of Duration of Treatment Resistance (DTR) may help to investigate whether shortening of DTR by optimizing medication schedules can further prevent long-term disability in patients with schizophrenia.

When defining DTR, we need to be aware of a complex and developing field concerning criteria for adequate treatment response, necessary doses of conventional antipsychotics, minimum duration of treatment, and adherence measurements before meeting the definition of TRS.

Firstly, based on all available evidence, consensus criteria for TRS have been formulated.[3] The authors acknowledge that defining treatment response with relative thresholds (a 20% decrease in symptoms measured by validated scales) raises methodological problems as TRS becomes dependent on symptom levels before treatment and suggest to focus on acceptable levels of residual symptom and impairment severity.[3] This is in line with Andreasen et al[6] that defines adequate treatment response as attenuation of symptom severity, below the level of inference with functioning. Therefore, we propose to define TRS as not achieving remission criteria of Andreasen et al[6]. The advantage of this definition is that it is applicable in practice, measurable and unrelated to symptom levels before treatment.[6]

Secondly, the dose of conventional antipsychotics needed in Recent Onset Schizophrenia (ROS) to achieve an adequate response is generally lower. While it is recognized that adequate dosing of conventional antipsychotics differ between ROS and chronic schizophrenia in most guidelines, this is not reflected in the suggested criteria of treatment resistance, where chlorpromazine equivalent doses of 600 mg are required for conventional antipsychotics in order to fulfill treatment resistance criteria.[3] These proposed dosing strategies in chronic schizophrenia patients could lead to intolerable side effects in ROS, of which we know that they do not outweigh potential benefits and contribute to unnecessary prolongation of inadequate treatment.

Finally, taking 6 weeks as a minimal treatment period per antipsychotic drug has been put into question, whereby at one hand, some literature points at a negligible chance of reaching response criteria at 6 weeks when patients have not improved at all after 2 weeks, and on the other hand, some patients have a delayed response exceeding 6 weeks.[3] Although a minimal treatment period of 12 weeks would currently be regarded as a very short period to determine TRS, unnecessary prolongation of an unsuccessful treatment should be regarded in the light of the guiding principle "primum non nocere."

By having more attention for DTR as the next challenge after early intervention treatment and research, the field needs to explore previously mentioned issues in order to determine if we should adjust our treatment guidelines in ROS in order to timely recognize TRS, without pursuing potentially harmful dosing strategies. Lastly, it is important to consider that different pathways to treatment resistance have been identified[2]: early TRS (patients not responding to 2 consecutively conventional antipsychotics from the start of the treatment) and late TRS (patients who cease to respond to conventional antipsychotics, constituting the minority of TRS patient), also known as tachyphylaxias.

With these facts in mind, we propose to define DTR as follows:

- In case patients never adequately responded to 2 adequate conventional antipsychotic trials, DTR is calculated as time between start of antipsychotic treatment and reaching remission criteria[6] on clozapine or another therapy.
- In case patients cease to react to previously successful treatment, DTR is calculated as time between the loss of effectiveness of conventional antipsychotic treatment and reaching remission criteria[6] on clozapine or another therapy.

We encourage the field to investigate DTR, its proposed remission criteria and required dosing strategies for ROS in future studies in order to gain knowledge about different aspects of treatment response and resistance. The possibility of a critical time window to optimally respond to clozapine in the course of schizophrenia needs to be explored prospectively, as well as to what extend shortening DTR promotes favorable disease course. Finally, discovering biomarkers that identify response potential to either conventional antipsychotics, clozapine, or other treatments remain direly needed.

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