ANTI-SCHIZOPHRENIA DRUGS: THE NEXT GENERATION

Gary Remington, George Foussias, Ofer Agid, Margaret Hahn, Hiroyoshi Takeuchi, Naren Rao

Gary Remington is a Professor of Psychiatry at University of Toronto and Director of Medication Assessment Program for Schizophrenia, Centre for Addiction and Mental Health, Toronto, Canada.

Periodically, it is useful to stand back and reflect on where we've been and where we're going. In the case of schizophrenia and its pharmacotherapy, we now have just over a half-century of experience behind us which includes a resurgence in interest over the last two decades, driven by clozapine's reintroduction and a host of new drugs attempting to mirror its clinical superiority while avoiding its more serious side effects (e.g. agranulocytosis, seizures).

Changes in terminology are themselves telling. We've transitioned from 'major tranquilizers' to 'neuroleptics' ("to take the neuron") to 'antipsychotics' which, knowingly or unknowingly, seems to have moved us in the right direction[1-4]. Yes, these drugs are calming, and certainly they "take the neuron", reflected in their various side effects (extrapyramidal symptoms being the hallmark of first generation agents). Most importantly though, these drugs have been revolutionary because they represented the first clearly established *anti-psychosis* agents that we had at our disposal.

Gary Remington, Professor of Psychiatry, University of Toronto and Director of Medication Assessment Program for Schizophrenia, Centre for Addiction and Mental Health, Toronto, Canada.

George Foussias, Institute of Medical Science, University of Toronto and Research Fellow, Complex Mental Illness Program - Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, Canada

Ofer Agid, Associate Professor, University of Toronto and Clinician Researcher, Complex Mental Illness Program - Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, Canada

Margaret Hahn, Research Fellow, Complex Mental Illness Program - Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, Canada

Hiroyoshi Takeuchi, Research Fellow, Complex Mental Illness Program - Schizophrenia Division, Centre for Addiction and Mental Health, Toronto, Canada

Naren Rao, Research Fellow, PET Centre, Centre for Addiction and Mental Health, Toronto, Canada

Correspondence:
Dr. Gary Remington
Centre for Addiction and Mental Health (CAMH)
Complex Mental Illness Program, Schizophrenia Division
250 College Street, Toronto, Ontario, Canada M5T 1R8
E-mail: gary.remington@camh.ca

Along the way, though, our conceptualization of schizophrenia has changed, and it has become patently evident that psychosis is only part of the story. By the early 1980's, for example, attention turned to a distinction between positive (e.g. hallucinations, delusions) and negative (used here, referring to 'primary' negative or 'deficit' e.g. amotivation, anhedonia) symptoms[5,6], which soon after included discussion of 'secondary' negative symptoms[7]. On the back of clozapine[8], we entered the 1990's with the belief that we now had *anti-psychosis* and *anti-negative symptom* drugs; moreover, they were to be better *anti-psychosis* drugs because clozapine worked where others failed.

Surely this would translate to improved functional outcomes. Unfortunately, while gains were reported, it became evident that efficacy in substantially altering functional outcomes remained elusive[9]. Attention turned to neurocognition, with evidence suggesting that cognitive deficits may represent the rate-limiting step in functional recovery[10]. The newer 'atypical' antipsychotics laid claim to improving cognition, but results were inconsistent and the magnitude of change was not clearly evident in the clinical setting[11,12]. In addition, what accounted for any improvements observed proved open to debate. Was it their different receptor binding profile (e.g. greater serotonin 5-HT_2 versus dopamine D_2 binding), or was it simply a matter of 'dopamine sparing', represented by compounds with D_2 transience[13], and possibly complemented by a downward trend in antipsychotic dosing that gained momentum with *in vivo* evidence from neuroimaging employing D_2 occupancy thresholds to empirically define optimal doses[14].

Complicating the picture further was a growing recognition that the degree of cognitive dysfunction observed in schizophrenia could not account for the extent of functional impairment observed clinically[15]. Including negative symptoms, in addition to cognitive symptoms, provided a more comprehensive explanation and underscored the complex interplay of these different domains[16-18]; for example, how can one adequately tap into cognitive function if someone is amotivated? Which comes first?

Nuances of the different domains add another layer of complexity. Cognition is no longer confined to neurocognition (and its varied dimensions); there is a

growing interest in social cognition, which also has important implications in measures of functional outcome[19]. In the case of negative symptoms, efforts are in place to better define its components and, thereby, underlying mechanisms. An example of this is the distinction between appetitive ("wanting") and consummatory ("liking") drives, which has challenged the longstanding notion that anhedonia characterizes schizophrenia[20]. That is, deficits in schizophrenia represent the former, not the latter.

Along similar lines, shifts in our conceptualization of schizophrenia have altered how we define response. The traditional approach, driven by clinical symptoms and in particular positive features such as hallucinations and delusions, has given way to multiple symptom domains, a greater appreciation of subjective measures (e.g. quality of life), and functional outcomes. These changes have already impacted the field substantially, and there is no clearer example of this than current thinking regarding the prominent functional deficits that characterize many individuals with schizophrenia.

For decades, we practiced under the notion that effective control of positive symptoms was the key to functional recovery. Indeed, there was a time when high-dose antipsychotic treatment was a mainstay in efforts to eradicate these symptoms[21]. We have softened on this position, reflected in current definitions of remission that actually allow for persistent, albeit diminished, positive symptoms[22]. There is now clear evidence that the trajectories of clinical and functional recovery do not parallel each other, in that sustained functional impairment can be seen despite substantive clinical improvement[9]. Current thinking highlights negative and cognitive symptoms as the rate-limiting step for this disconnect[16-18], which has profound implications regarding treatment intervention and drug development. Such a change in thinking has taken on even more importance through the growing emphasis on recovery-based models of care[22], which demand that we take a broader based approach to defining response and outcome than our historical emphasis on symptoms.

On this point, though, most clinicians are likely to agree that it would be misguided to dismiss the impact of positive symptoms. Long-term psychiatric beds are still populated by individuals who remain poorly controlled in terms of positive symptoms, the so-called treatment-resistant and ultraresistant subpopulations[23]. Despite a host of new antipsychotics, clozapine remains unique in its efficacy for the former[24], although we still do not know what part(s) of its pharmacology account for this. In contrast, we really have no effective treatments for ultraresistant patients (i.e. those who have failed to respond to clozapine); there is a lack of compelling data to support our current strategy of augmenting clozapine treatment[25]. Simply put, we do this more out of hope than evidence.

Taking stock of our present position, where do we find ourselves? Schizophrenia is no longer seen as a unitary and distinct entity as might have been imagined by Kraepelin, defined collectively by its early onset and progressive deterioration[26]. Rather, we now talk of schizophrenia as a heterogeneous group of disorders, with different onsets, presentations, treatment response, trajectories, and outcomes. That DSM-V is moving us in the direction of a dimensional approach, with a psychosis phenotype[27], speaks to this issue. By the same token, how we view the illness itself, as well as treatment objectives and response, demands a different approach. Psychosis, once the defining feature, finds itself taking a back seat to other symptom domains as we shift our focus away from symptom based-definitions of outcome and talk more about functioning and recovery, Undoubtedly, this is related in part to the fact that it is positive symptoms for which we have the one established and reasonably effective treatment, but there are other reasons. There is ample evidence that, chronologically, the onset of psychosis is less reflective of the beginning of the illness than it is of the end of the illness as it declares itself, at least in terms of symptom evolution. Numerous studies inform us that negative as well as cognitive (both neuro- and social) symptoms predate the onset of psychosis[28-30].

Returning to our title, these changes in thinking require us to reframe how we talk about the treatment of schizophrenia. The many drugs currently available to us are *anti-psychosis* drugs; yes, they may provide modest improvements from the standpoint of other symptom domains but the extent of these gains is modest at best. They have not proven to be effective *anti-negative* symptom or *anti-cognitive* dysfunction drugs, at least in a way that translates to notable changes clinically. This is said with the recognition that current antipsychotics are increasingly used for other psychiatric diagnoses, both indicated and off-label[31,32]. Several points warrant comment here. These drugs can have other effects - we are reminded once again that they were initially referred to as 'major tranquillizers', which implies efficacy in symptoms that extend beyond psychosis per se (e.g. affect, anxiety). They do appear to provide benefits in this regard for individuals with schizophrenia, for example the anxiety/agitation often associated with active psychosis, but the extent of concomitant psychotropic drug use in schizophrenia, including both antidepressants and anxiolytics[33], would argue against their stand-alone efficacy for these specific diagnoses. On a more practical level, any use of these medications for symptoms beyond psychosis must be carefully weighed against their significant side effect profile. And, once again, evidence clearly suggests they are not particularly effective in treating negative (deficit) or cognitive symptoms[11,12,34].

On one hand, reconceptualizing schizophrenia as an illness of multiple symptom domains injects an entirely new level of hope and opportunity for the field. Despite numerous, multi-directional efforts , psychosis remains couched in the hyperdopaminergic model, and to date D_2 blockade remains the only aspect of antipsychotic pharmacology categorically linked to the efficacy of these drugs in this regard[14]. The notion, though, that this line of investigation can be put to rest is not the

case; those individuals partially or non-responsive to current antipsychotics are a clear reminder that at least some forms of psychosis are mediated by other mechanisms. In looking at these other symptom domains, though, there is no need to feel wed to dopamine or its blockade. There is good reason that it will also play a role, for example in negative symptoms given the amount of preclinical and clinical evidence implicating it in reward-related behaviour[35], but the door is wide open in terms of embracing other systems and mechanisms of action. This holds true for both negative and cognitive symptoms, which presents exciting opportunities that are already garnering research and putative agents[36].

On the other hand, our optimism may be tempered by an extensive body of evidence, within and beyond schizophrenia (e.g. Alzheimer's, Parkinson's disease), failing to demonstrate effective pharmacological strategies to enhance cognitive dysfunction or negative symptoms such as apathy. Certainly, within schizophrenia success with strategies that move us beyond dopamine in treating these domains has not been forthcoming. This is not to say gains have not been made, but again the magnitude of the improvement has generally been modest. In this vein, we must remember that we are late to the game in treating these symptoms. They are identifiable during the prodrome, but without specific biomarkers diagnosis routinely does not occur until psychotic symptoms appear, and even then treatment can be delayed considerably[37]. Whether earlier pharmacological intervention would lead to better outcomes in specific domains such as cognition and negative symptoms has not been clearly established, and we also cannot ignore the potential value of non-pharmacological interventions.

What does all this mean for the treatment of schizophrenia? First and foremost, it forces us to look beyond psychosis in assessing and managing this illness, and as part of the process outcome evaluation must expand beyond clinical symptoms to include other components considered relevant to daily living (e.g. functioning, subjective well-being). In terms of treatment, symptom resolution is ideal but remission now accommodates symptoms and adapts a more global perspective that takes us beyond psychosis. We have reasonably effective *antipsychosis* drugs, including clozapine in the case of refractory schizophrenia, but at present we have little to offer when clozapine fails.

Given the diversity of schizophrenia's symptoms, it seems naïve to imagine a drug that will be effective across the different domains (i.e. the "magic bullet" approach). More likely, greater gains will occur with an approach that looks for discrete agents addressing the different symptoms clusters, which can then be used in combination. In fact, this very much aligns with the notion of disease heterogeneity and the current interest in "individualized" medicine. This shift in treatment has been acknowledged by regulatory agencies such as the United States Food and Drug Administration (FDA)[38], and is reflected both in current drug development and ongoing trials where considerably more attention is being paid to 'add on' strategies (e.g. see, for example, *clinicaltrials.gov* for current examples).

With opportunities come challenges. Staying abreast of current thinking regarding schizophrenia and its treatment is now very much a dynamic process, a "work in progress" that requires clinicians on the front line to have a much broader understanding of the illness, its symptoms, and diagnostic/treatment strategies. An adequate assessment now takes us well beyond the clinical interview, and calls for multi-disciplinary expertise. Pharmacologically, we must divest ourselves of the notion of a "one diagnosis-one drug" approach. To some extent we are already familiar with this, often drawing upon other classes of medications (e.g. mood stabilizers, antidepressants, anxiolytics) as part of our treatment. In a sense, the illness is being "de-centralized" as thinking shifts to incorporate functional recovery, where evidence tells us that other domains are as important as psychosis, if not more so. The next generation of "anti-schizophrenia" drugs is less likely to reflect single agents trying to do all things, but instead combinations of agents that work discretely on the various key subdomains of schizophrenia (i.e. positive, negative, cognition), balanced according to a particular individual's clinical picture and complemented by non-pharmacological interventions.

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