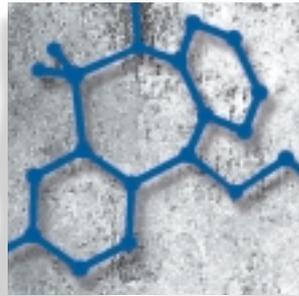


## Treatment-refractory schizophrenia

Asaf Caspi, MD; Michael Davidson, MD; Carol A. Tamminga, MD



*Between one-third and one-half of the individuals who meet diagnostic criteria for schizophrenia remain actively ill despite optimal pharmacological treatment. These individuals tend to progressively deteriorate in terms of social and vocational functioning despite major public and private investments in their rehabilitation. For patients who do not respond to the first prescribed antipsychotic drug, current clinical practice is to switch to a second and a third drug, and eventually to clozapine, the only antipsychotic drug proven to be effective in treatment-refractory schizophrenia (TRS). Occasionally, two antipsychotics are given concomitantly or psychotropic drugs are added to antipsychotic drugs; however, very few empirical data exist to support this practice. Although there are many exceptions, patients who do not benefit from the first prescribed drug will not benefit from any pharmacological intervention. Therefore, efforts are under way to determine the reason for lack of response to available treatments and devise novel, more effective treatments. To be successful these efforts must result in a more specific definition of TRS, as well as in a better understanding of the illness pathophysiology and the mechanism of action of the drugs.*

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**D**espite the proven efficacy of antipsychotic medications and despite the additional advantages of the new-generation antipsychotics,<sup>1,5</sup> one-fifth to one-half of schizophrenia patients are classified as refractory to pharmacological treatment<sup>6-13</sup> and this proportion remains consistent over time.<sup>3</sup> The management of treatment-refractory schizophrenia (TRS) is a persistent public health problem, because a substantial number of inpatient psychiatric beds<sup>14</sup> and resources are devoted to these patients,<sup>15</sup> and because they experience the worst outcomes, such as suicide<sup>16</sup> and homelessness.<sup>17</sup> TRS can manifest itself as failure to achieve remission from the initial episode of psychosis, failure to maintain remission, or gradual deterioration in the context of successive relapses.<sup>18</sup> For classification and descriptive purposes, as well as for enrollment into trials of experimental treatments, TRS patients are grouped on the basis of predefined criteria. However, there is considerable variability within this population, in terms of specific domain of treatment refractoriness as well as degree of refractoriness (severity of persistent symptoms).

### Defining treatment refractoriness

Since treatment with antipsychotic drugs has been the most accepted and effective treatment intervention in schizophrenia over the last 40 years, the traditional def-

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inition of TRS was driven by response to such treatment. This definition includes chronic illness and failure to achieve a decline in Brief Psychiatric Rating Scale (BPRS) score of between 20% and 30% despite two adequate treatment trials with antipsychotics from two different classes.<sup>19</sup> A 4- to 6-week trial of 400 to 600 mg/day chlorpromazine or its equivalent is currently accepted as the standard for an adequate treatment trial.<sup>20-22</sup> Interestingly, although the original definitions of TRS require failure to respond to treatment with two drugs, there is evidence that failure to respond to one drug is strongly predictive of failure to respond to the second drug.<sup>23,24</sup>

Starting in the late 1970s and 1980s, the diagnostic systems (*Diagnostic and Statistical Manual of Mental Disorders [DSM]* and *International Classification of Diseases [ICD]*) have been continually revised to reflect a more narrow definition of schizophrenia with psychosis as a central feature. Interestingly, this corresponds to the period when antipsychotic drugs have fully penetrated daily clinical practice. No wonder, therefore, that treatment success and treatment refractoriness were defined as a function of these drugs' ability to suppress psychotic symptoms. During most of the 1990s, the focus of schizophrenia research and treatment has moved from psychosis towards enduring negative symptoms,<sup>25,26</sup> cognitive impairment,<sup>27-31</sup> and recently, quality of life<sup>32,33</sup> and social reintegration.<sup>34-36</sup> Interestingly, the more recent definition of TRS has raised the bar to include the persistence of moderate-to-severe positive and negative symptoms together with the persistence of other symptoms such as cognitive, social, and occupational impairments and behavioral problems.<sup>37,38</sup> This definition, in addition to the expectation that the novel antipsychotics will distinguish themselves from the classic ones and among themselves, has changed treatment expectations and redefined treatment outcome to encompass these domains.

Some of the difficulty associated with the definition of TRS derives from the confusion between illness severity, chronicity, and illness sequels. Using the broadest definition of TRS would imply that any persistence of any symptom, or abnormal behavior or sequel, would qualify for treatment refractoriness. For example, an adolescent who before the first psychotic episode had been socially and vocationally successful, but who has not returned to the previous level of functioning despite adequate and extensive treatment, could be considered as suffering from TRS.

In summary, because of the syndromal nature of schizophrenia, and the heterogeneous response to treatment, classifying a patient or a cohort as TRS has little descriptive or empirical value. For example, patients can be defined as suffering from TRS for the purpose of enrolment into an intervention trial, or for the purposes of deciding the level of disability compensations and support need with activities of daily living (ADLs). Hence, depending on the purpose of the definition, the criteria for TRS must reflect the specific domain(s) of refractoriness, its severity, and previous treatment attempts.

## Mechanisms of TRS

Since it became clear that a significant proportion of patients do not respond to available treatments, clinicians and investigators attempted to predict nonresponse to treatment as early as possible and explain the mechanisms of TRS. However, this attempt has been fraught with both scientific and conceptual difficulties.

Epidemiological data have revealed that male gender,<sup>8,39,40</sup> early age of onset of illness,<sup>41-43</sup> positive family history of schizophrenia,<sup>44,45</sup> obstetric complications,<sup>46</sup> absence of affective symptoms,<sup>47</sup> severe and lengthy premorbid manifestations,<sup>39,45,48,49</sup> longer duration of untreated psychosis,<sup>50,51</sup> severe negative and cognitive symptoms,<sup>52,53</sup> presence of soft neurological signs, early onset of abnormal involuntary movements,<sup>54</sup> and low level of social functioning<sup>55</sup> were all associated with some degree of treatment refractoriness. However, the reported associations have generally been weak and inconsistent. Furthermore, even if the associations were stronger and more consistent, they would not necessarily constitute early predictive markers or explanatory mechanisms since too often they are epiphenomena, and consequences of TRS. For example, poor social functioning in an individual whose TRS illness started at an early age before he or she had an opportunity to acquire social and vocational skills is a result of the early and persistent illness, rather than an explanation or a predictor of TRS. Ventricular<sup>56-58</sup> and cortical sulci enlargements<sup>57,59,60</sup> abnormal cell migration in the prefrontal cortex,<sup>61</sup> cavum septum pellucidum,<sup>62</sup> and abnormal (lower) cerebrospinal fluid (CSF)<sup>63</sup> and plasma catecholamine concentrations<sup>64</sup> are some of the biological markers associated with TRS. Unfortunately, most of these findings are the result of post hoc subgroup analysis generally derived from studies failing to demonstrate the a priori hypoth-

esized biological abnormality in the entire sample. In fact, most of the post hoc findings have not been consistently replicated or demonstrated in a priori designed studies. Despite the conflicting data—or maybe because of the conflicting data—theoretical formulations have been advanced to explain TRS. Both the developmental and the degenerative conceptualizations of schizophrenia have been invoked to explain TRS.<sup>65</sup> An immutable, genetically mediated process or one mediated by an early developmental insult can confer characteristics that are not responsive to available treatment, but are not necessarily related to psychosis. For example, being born with a medium-to-low intelligence quotient (IQ) would create the impression of TRS in a psychotic patient, even after the psychosis improves. Similarly, a degenerative process might confer the refractoriness to treatment. In fact, TRS very rarely develops after the first or second episode, but rather after several episodes and several years of illness. Only 10% to 15% of schizophrenia patients are treatment refractory at the onset of disease,<sup>8</sup> while nearly one-half eventually become treatment refractory. Taken together with the imaging studies reporting progressive degeneration of brain parenchyma in TRS patients,<sup>66</sup> these data are at least consistent with a degenerative process.

While the biological mechanisms of TRS (like the mechanism of schizophrenia in general) remain elusive, there are a number of environmental and conceptual explanations for TRS. Poor compliance with drug treatment is a frequent problem among schizophrenia patients. Side effects such as extrapyramidal symptoms (EPS), sexual dysfunction, and weight gain,<sup>67-69</sup> along with lack of insight are the leading causes of noncompliance. Apparently, physicians often underestimate the nonadherence of their patients, which in turn does not allow them to consider nonadherence as a probable explanation for treatment refractoriness. Hence, some of the patients classified as TRS may not actually be on medication. Use and abuse of illicit drugs, alcohol, and prescription medications (such as anticholinergic agents) might obscure, impede, or diminish the therapeutic effect of antipsychotics, further increasing the proportion of TRS patients.

Distinguishing between TRS, consequences, and complications of illness, as well as non-illness-related maladaptive behaviors further complicates the understanding of TRS. For example, poor social adjustment due to interruption of vocational training, stigma, and demoralization, poor hygiene, and unhealthy lifestyle all con-

tribute and add up to give the appearance of TRS. Furthermore, a tendency to attribute any maladaptive behavior, such as antisocial or deviation from cognitive performance norms, to the schizophrenic illness in an individual carrying a diagnosis of schizophrenia, further enhances the appearance of TRS. For example, although the premorbid distribution of cognitive performance scores is mildly shifted to the left (worse) in schizophrenic patients, and although for some individuals it could be linked to the schizophrenic illness, the IQ distribution contains very severely impaired patients, mostly individuals of average intelligence, as well as some very intelligent patients. This is consistent with the notion that some cognitive deficiencies are related to the illness, while most others are not. Yet cognitive deficiency, whenever present, is attributed to the schizophrenic illness and pharmacological interventions are targeted toward improving it. Furthermore, exaggerated expression of normal frustration with the hurdles of daily life is often viewed as illness-related aggression. Failure to improve cognitive performance or altered maladaptive behavior is often viewed as evidence for TRS. Finally, even though various degrees of depressed mood and anxious mood are very prevalent in patients suffering from schizophrenia, they could be merely secondary to a daily struggle and frustration associated with a chronic mental disease, rather than a primary manifestation of disease. Regardless of whether some or all of these manifestations are an integral part of the schizophrenic illness, complications, or comorbidities, they add to the appearance of TRS.

In summary, progress in defining the boundaries of TRS and distinguishing between primary illnesses-related manifestations and the complications and consequences of illness might both improve the yield of treatment and prevent unnecessary treatment. More important, the solution to TRS is closely dependent on understanding the biology of schizophrenia in general. Meanwhile, the immediate treatment needs of TRS must be addressed with the available knowledge and tools.

## Treatment of TRS

Verifying compliance by measuring neuroleptic plasma level or prolactin levels should be the starting point in the treatment of a TRS patient. Reconsidering doses and dosing should follow so that EPS and akathisia are not confounded with TRS. Assessing and treating psychiatric

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comorbidities and medical comorbidities should follow. Nonpharmacological, social, family, and personal needs that might affect illness manifestation and nonresponse to treatment should be addressed.<sup>70-73</sup> Realistic treatment targets, which consider the premorbid (often poor) functioning, should then be set. It is essential to remember that in an illness that is by definition chronic, such as schizophrenia, response is a relative term and that many patients continue to suffer from low-level symptoms even after a significant response to treatment has occurred.

Biological treatment for TRS patients is centered on the use of clozapine or newer atypical antipsychotics, augmentation drug therapies, and the combination of antipsychotics with electroconvulsive treatment (ECT). These strategies have been well reviewed elsewhere<sup>37,74,75</sup> and thus will be briefly summarized here. However, before reviewing each individual intervention, it is essential to consider the inherent difficulties in conducting trials in TRS patients and hence providing good scientific data to address this prevalent problem. Trials in TRS patients are longer and more laborious, the population is difficult to agree upon and even more difficult to recruit. More importantly, when strategies in which an active compound or placebo is added to an antipsychotic (adjunctive therapy or augmentation) are evaluated, the sample size necessary to obtain valid results is extremely large—a fact that further increases the effort and the cost of the trial.<sup>76</sup>

Moreover, due to pharmacokinetic interactions, add-on trials present difficulties in interpreting the results. It is often difficult to determine whether the advantage of the added compound is due to an intrinsic property of the added compound or due to changing the blood concentration of the concomitantly administered medication. Because of the difficulties conducting prospective trials in TRS patients, clinicians often base their practice on consensus algorithms. Unfortunately, these algorithms are too often based on impressionistic data rather than on randomized clinical trials.

## Clozapine

Despite some recent reservations, clozapine remains the gold standard for the treatment of TRS, being the only drug with proven superiority to both chlorpromazine in rigorously defined TRS<sup>19</sup> and other classic neuroleptics.<sup>21,77</sup> Furthermore, clozapine was found to be effective in reducing violent behavior,<sup>78,79</sup> and the risk of suicide.<sup>16,80,81</sup>

Nevertheless, a recently published meta-analysis suggests that, despite its reputation, most recent studies did not support the superiority shown by clozapine in early trials.<sup>82</sup> Furthermore, although more TRS patients benefited from clozapine compared with previous antipsychotic treatment, between 50% and 70% of the TRS patients did not significantly benefit from the switch to clozapine.<sup>42,83</sup> In particular, most recent trials indicated that the differential reduction in BPRS scores favoring clozapine was very small and of questionable clinical significance. Additional remarks on treatment with clozapine are noteworthy. Some of the benefits of treatment with clozapine become evident on long-term follow-up. Some studies have shown that a subset of TRS patients need longer periods than the usual 6 to 8 weeks of adequate dose<sup>84,85</sup> to show a significant response.<sup>16,42,86</sup> Furthermore, patients who do not respond under a regular dose may respond to high doses that bring their plasma level higher than 350 ng/mL.<sup>87</sup>

A still unresolved question is whether clozapine does indeed have unique intrinsic properties that make it effective in TRS or whether its higher efficacy over the classic antipsychotics is secondary to its better tolerability (no EPS and an upper ceiling for doses). In fact, the possibility that clozapine might have unique intrinsic properties that confer its advantage over the rest of the antipsychotics has generated a large number of investigations to elucidate its mechanism of action. Its relatively weaker affinity for, and lower occupancy of, nigrostriatum dopamine D<sub>2</sub> receptors, its D<sub>2</sub>/5-HT<sub>2</sub> (serotonin receptor) ratio, its anticholinergic and cholinomimetic activities, as well as its selectivity for putative brain areas have all been suggested to explain clozapine's unique clinical properties. Despite the fact that no agreement exists as to what mechanism mediates clozapine's unique clinical profile, most of the novel antipsychotic drugs were modeled on it.

## Novel atypical agents

The availability of a generation of novel antipsychotics modeled on clozapine has raised expectations that they will be effective in treating TRS. In fact, many of the patients who were treated with the novel drugs were initially partial responders or TRS patients. Studies showed better efficacy of risperidone,<sup>88-90</sup> olanzapine,<sup>91-95</sup> quetiapine,<sup>96</sup> and recently ziprasidone<sup>97</sup> in TRS patients or partial responders compared with typical agents. However,

the differential efficacy was modest,<sup>5,98</sup> some of the studies had methodological limitations such as less rigorous definitions of TRS<sup>91-94,99-101</sup> and of what constitutes response, open-label and retrospective designs,<sup>88,89</sup> and small sample size.<sup>99-101</sup> A corollary attempt to examine if the novel antipsychotics are effective in TRS patients was to treat aspects of schizophrenia that tend not to respond to classic drugs, such as the negative symptoms and the cognitive impairment. Initial results have suggested an advantage for cognitive impairment<sup>29,102-105</sup> and for negative symptoms,<sup>95,106-110</sup> but these advantages have not been consistent across trials.<sup>19,42,86,111-114</sup>

### Combined antipsychotic drugs

The assumption that broader or higher level of receptor binding could lead to improved efficacy of antipsychotics constitutes the rationale behind the use of combined antipsychotic therapy. While the use of this approach is growing along with the frequent use of polypharmacy in schizophrenia patients (estimated 20%),<sup>115</sup> little research is available to support it. The data derive mostly from case reports and open studies indicating improved efficacy of clozapine treatment following the addition of risperidone,<sup>116-122</sup> olanzapine,<sup>123</sup> or typical agents, such as pimozide and sulpiride.<sup>124-126</sup> However, the rationale behind this strategy remains elusive and the supportive data are doubtful. Selecting polypharmacy regimens according to specific symptoms or on the basis of a putative mechanism of action is way ahead of the current state of basic knowledge of schizophrenia pathophysiology and the recognized mechanism of action of drugs. Furthermore, occasionally, the rationale for combined antipsychotic treatment contradicts the current theories on mechanisms of action of drugs. Such is the case with the use of adjunctive antipsychotics and clozapine. While some of the presumed advantages of clozapine are related to its limited D<sub>2</sub> antagonism, prescribing adjunctive antipsychotics transforms clozapine into a classic drug.

### Antidepressants

Since depressed mood, residual depression, or even demoralization are often taken as unsatisfactory response to treatment, antidepressants are extensively used as adjunctive treatment to antipsychotics in schizophrenia. Most of the data on the use of antidepressants

are derived from trials with selective serotonin reuptake inhibitors (SSRIs), which have occasionally,<sup>127-131</sup> but inconsistently,<sup>132</sup> showed efficacy. At present, there is no convincing evidence to support or refute the use of antidepressants in treating depression in schizophrenia<sup>133,134</sup> and no substantial evidence to support the use of these agents for the treatment of refractory negative symptoms. Furthermore, the question of whether it is possible to distinguish between comorbid major depression, depressive symptoms, demoralization, anhedonia, and persistent negative symptoms remains open.

### Mood-stabilizing drug treatments

Most of the data on adjunct medications are on lithium and anticonvulsants. Several studies indicated a beneficial effect of lithium in TRS patients.<sup>135-138</sup> However, these studies used loose definitions of TRS and small samples. Definitive evidence of a significant efficacy of lithium has not been presented yet. This could be because the preliminary trials are not sufficiently encouraging or because there is no sufficient commercial incentive to invest in a large (expensive) trial to provide definitive evidence. Studies on anticonvulsants as adjunct therapy for TRS yielded contradicting findings on valproic acid<sup>139,140</sup> and modest effects in controlled studies with small samples on adjunct carbamazepine.<sup>16,141,142</sup> Data on novel anticonvulsants (topiramate and lamotrigine) is limited to case studies.<sup>143</sup> While anticonvulsants are widely used, there are few controlled trials on their efficacy. Furthermore, anticonvulsants and lithium are prescribed for violent behavior, although evidence is scarce. Unlike the purposeless violence in temporal lobe epilepsy, there is no reason to believe that violence in schizophrenia has a specific illness-related biological mechanism. If carbamazepine can be effective in treating the violent outburst of TRS, this is probably the result of a nonspecific non-illness-related effect. Hence, it is essential to demonstrate first that the drug is effective in treating violence across diseases as well as primary violence before using it in TRS.

### Electroconvulsive therapy

ECT given concomitantly with antipsychotic drugs was shown to have some effect on TRS in a few short-term trials and case reports.<sup>144-151</sup> However, it is important to note that patients who get ECT are the more severe

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patients, and they generally get ECT after most other interventions have failed. Hence, when and if improvement is eventually associated with ECT, the possibility of a regression to the mean of the most severe patients cannot be ruled out. Moreover, the lack of controlled trials remains the main disadvantage of research in ECT, and despite nearly six decades of wide clinical use, a strong substantial support is still absent. Furthermore, issues such as the persistence of effect and the long-term maintenance of TRS patients treated with ECT have not been adequately addressed.

## Conclusions

TRS remains a major personal tragedy and a public health problem. However, because so little is known about TRS and because the results of treatment are so

variable, it is essential to weight carefully the risk-benefit ratio. Although atypical novel antipsychotics are better tolerated than older drugs and may be more effective in some but not most TRS patients, no proven treatment exists for TRS. It is essential that, instead of increasing the dose and relentlessly adding and changing medications, or embarking upon unproven interventions, psychiatrists acknowledge to themselves and explain to frustrated patients and family members, the limits of pharmacological treatment. Otherwise, we run the risk of making a bad situation worse by adding the suffering of adverse effects to that of the illness.

Hopefully, persistent investigation should lead us to where other medical disciplines are, by which putative drugs developed based on pathophysiological understanding will treat specific manifestations of this syndromal disease. □

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### Esquizofrenia resistente al tratamiento

Entre un tercio y la mitad de los individuos que cumplen con los criterios diagnósticos para esquizofrenia permanecen con la enfermedad activa a pesar de un tratamiento farmacológico óptimo. Estos sujetos tienden a deteriorarse progresivamente en términos del funcionamiento social y vocacional a pesar de las grandes inversiones públicas y privadas en su rehabilitación. Para los pacientes que no responden al primer fármaco antipsicótico prescrito, la práctica clínica actual consiste en cambiar a un segundo y a un tercer fármaco, o como último recurso en administrar clozapina, el único fármaco antipsicótico que ha probado ser efectivo en la esquizofrenia resistente al tratamiento (ERT). En ocasiones se han indicado dos antipsicóticos en forma simultánea o se han agregado otros psicotrópicos a fármacos antipsicóticos; sin embargo, existen muy pocos datos empíricos que sustenten esta práctica. Aunque hay muchas excepciones, los pacientes que no se benefician con el primer fármaco prescrito tampoco se beneficiarán con alguna otra intervención farmacológica. Por lo tanto, los esfuerzos deben orientarse a determinar la razón de la falta de respuesta a los tratamientos disponibles y diseñar nuevos tratamientos más efectivos. Para tener éxito, estos esfuerzos deben conducir a una definición más específica de ERT y a una mejor comprensión de la fisiopatología de la enfermedad y de los mecanismos de acción de los fármacos.

### Schizophrénie réfractaire au traitement

Un tiers à la moitié des personnes qui répondent aux critères diagnostiques de schizophrénie continuent à présenter une maladie active malgré un traitement médicamenteux optimal. L'état de ces sujets a tendance à se dégrader progressivement en termes de fonctionnement social et professionnel malgré des investissements privés et publics importants pour leur réadaptation. Pour les patients qui ne répondent pas au premier neuroleptique prescrit, la pratique clinique habituelle est de passer à un deuxième puis à un troisième médicament et finalement à la clozapine, le seul neuroleptique dont l'efficacité dans la schizophrénie réfractaire au traitement (SRT) a été démontrée. Dans certains cas, deux neuroleptiques sont donnés de façon concomitante ou bien des psychotropes sont ajoutés aux neuroleptiques ; cependant, très peu de données empiriques existent pour étayer cette pratique. Malgré de nombreuses exceptions, les patients qui n'ont pas été améliorés par le premier médicament prescrit ne le seront généralement pas plus par une autre intervention pharmacologique. Cette situation explique les efforts en cours pour déterminer la raison du manque de réponse aux traitements existants et pour développer de nouveaux traitements plus efficaces. Pour être couronnés de succès, ces efforts doivent se traduire par une définition plus précise de la SRT, ainsi qu'une meilleure compréhension de la physiopathologie de la maladie et du mécanisme d'action des médicaments.

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