Treatment Resistant Schizophrenia (TRS)

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Outline of the presentation

- Introduction
- Prevalence and Clinical Characteristics
- Operational definitions and Algorithm definitions
- Clinical and biologic correlates of treatment response
- Neuroimaging correlates of TRS
- Treatment options for TRS
  - Pharmacological and Nonpharmacologic Strategies
- Summary

Introduction

- History of psychiatry, antipsychotics introduction represent a major milestone
- Discovery of chlorpromazine (CPZ) brought high hopes in 1950s
- From outset of CPZ use, a specific group were considered refractory or resistant to phenothiazine
- Definition proves problematic as schizophrenia is chronic disease and 80-90% develop some social/occupational dysfunction (Meltzer et al, 1990)
- Chronicity vs. refractoriness
- Conley and Kelly, 2001 pointed out poor compliance, weak social support, h/o violence can keep patients chronically hospitalized without having TRS
Introduction

- Response is a reduction in the severity of Sx, as assessed by some sort of scale
- Remission means almost total absence of Sx for a certain period of time
- Recovery is absence of disease for a long period
- Remission in schizophrenia is defined as a minimum period of 6 mos. during which psychotic sx, disorganization sx and neg sx have low levels of clinical severity cor to levels of 3 or less on BPRS or PANNS
-TRS is sometimes associated with remission, but is also related to response

Prevalence and Clinical Characteristics of TRS

- Hegarty et al in 20th century observed that after introduction of neuroleptic therapy, only 48% pts who had chronic schizophrenia had favorable outcome and approx 20% of 1st episode did not respond to conventional antipsychotic after 1yr of treatment (meta-analysis)
- Meltzer et al observed mean diff. of 2 yrs at disease onset with male predominance
- Henna and Elkis observed male predominance with higher hosp.
- AAO for TRS patients was around 17yrs compared with around 20 yrs who responded to Rx.
- Other correlates: no. of episodes, long DUP and h/o substance abuse

Prevalence and Clinical Characteristics

- Psychopathology – authors assessed homogenous populations who had TRS using well known rating scales (PANSS, BPRS) to detect symptom clusters
- Lindenmayer et al used PANSS to evaluate 157 pts who had TRS and found a factor structure who were responsive to Rx: pos, neg, excitement, cog. and depressive factors
- Mcmohan et al used BPRS and observed through confirmatory analysis that 13 of 18 items loaded into 4 factors: reality distortion, disorg., neg. sx and anxiety depression.
- Above authors proposed such factors should be used in analyzing data from clinical trials involving patients who have TRS

Operational definitions of TRS

- Definition of TRS is multidimensional and a simple dichotomous definition is inadequate
- Some authors have tried to construct operational definitions based on one dimension such as symptom reduction
### Early Operational Criteria for treatment resistant schizophrenia

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Criteria</th>
<th>Instrument</th>
</tr>
</thead>
<tbody>
<tr>
<td>Csernansky et al, 1983</td>
<td>Past response to antipsychotics based on reduction of items of scale</td>
<td>10 item chart review scale</td>
</tr>
<tr>
<td>May et al, 1988</td>
<td>Response based on a scale developed by author</td>
<td>6 item scale of remission or recovery ranging from excellent (1) to refractory (6). Each item has 2 dimensions: clinical and social</td>
</tr>
<tr>
<td>Wilson, 1989</td>
<td>Psychotic symptoms persisting for more than 2.5 years after treatment with 3 neuroleptics of different classes (1000mg CPZ eq) for 6 weeks within last 5 yrs</td>
<td>BPRS≥ 45 (with severity in items such as hallucinations, delusions, thought disorders as or more severe as other items)</td>
</tr>
<tr>
<td>Keefe, 1991</td>
<td>No sufficient improvement after neuroleptic treatment</td>
<td>40mg haloperidol/d during 6 weeks</td>
</tr>
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</table>

### Operational criteria continued

- Operational criteria most widely used for definition of TRS are those of Kane and colleagues
- Kane’s criteria enabled the selection of patients who had TRS for the study that introduced clozapine for the therapeutic armamentarium for schizophrenia, which paved the way for emergence of SGAs.

### Original criteria for treatment resistant schizophrenia used in clozapine trial (Kane et al)

<table>
<thead>
<tr>
<th>Historical</th>
<th>Actual</th>
<th>Prospective</th>
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<tr>
<td>At least three treatments with antipsychotics of at least 2 different chemical classes with doses equivalent to 1000 mg/d of chlorpromazine for a period of 6 weeks, without significant relief</td>
<td>A score of at least 45 in the BPRS (1–7 degrees of severity) with scores of at least 4 in two of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, or unusual thought content</td>
<td>No improvement after 6 weeks of treatment with haloperidol (up to 60 mg/d or higher); improvement is defined as a 20% reduction of the BPRS as compared with the level of severity defined by the actual criteria and/or</td>
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<tr>
<td>No period of good function within the preceding 5 years</td>
<td>CGI ≥ 4 (moderately ill)</td>
<td>A post treatment CGI of ≤ 3 or a BPRS ≤ 35</td>
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</table>

### Algorithm definitions of TRS

- APA, Schizophrenia(POR) or TMAP stated- A pt. who has not responded to 2 or 3 treatments using atypical antipsychotics for a duration of 4-6 weeks can be considered as having TRS and eligible for Rx with clozapine
- Schizophrenia Algorithm of the International Pharmacological Algorithm Project (www.ipap.org) states that a patient who has not responded to 2 trials of 4-6 weeks duration using monotherapy with 2 different SGAs (or 2 trials with an FGA) is considered to have TRS and is eligible for treatment with clozapine for a 6 month trial with doses up to 900 mg/day.
- The algorithm is as follows:
Clinical and biologic correlates of treatment response

- A recent evidence-based review by Kinon and colleagues recommends the following oral doses for SGA:
  - Risperidone: 4 to 6mg/d
  - Olanzapine: 10 to 20mg/d
  - Quetiapine: 300 to 600mg/d
  - Ziprasidone: 80 to 160mg/d
  - Aripiprazole: 15 to 30mg/d

- The majority of guidelines recommend an antipsychotic agent be used for a minimum of 4 weeks before considering switching to another antipsychotic medication.

Neuroimaging Correlates of TRS

- Sheitman and Lieberman propose two forms of treatment resistance:
  - One that is present at the onset of the illness and another that evolves as the illness progresses.

- Combining neurodevelopmental and neurodegenerative aspects of the evolution of schizophrenia, the authors propose that TRS develops according to three stages:
  - Cortical pathology and deficient neuromodulatory capacity resulting from genetic/epigenetic etiologic factors occurring during childhood
  - Neurochemical sensitization leading to dopamine release
  - Neurotoxicity with consequent development of structural neuronal changes in adulthood
Neuroimaging Correlates of TRS continued

- It is conceivable that brain abnormalities may underlie the development of resistance in schizophrenia.
- The relationship between structural brain abnormalities and response to conventional antipsychotic treatment was the subject of pioneer studies.
- However, Friedman and colleagues in a meta-analysis of CT studies published that brain abnormality was not predictive of treatment response (between 1980-1989).
- In an 18 month follow up study, Lieberman and colleagues observed an increase in ventricular dimensions among patients classified as non-remitters when compared with controls or remitters.

Treatment Options for TRS

- Pharmacologic Treatments:
  - Beginning in late 1970s-1980s therapeutic attempts were made by using endorphins, prostaglandins, lithium and FGAs but none of these treatments proved effective.
  - With the advent of clozapine in 1988 (Kane et al), it became the standard of treatment for TRS.
- Meta-analyses of controlled trials involving patients who had TRS and systematic reviews showed that clozapine is as effective or is more effective than other SGAs for treating TRS.

<table>
<thead>
<tr>
<th>Author et al, yr</th>
<th>Type of Review</th>
<th>Controlled Trials</th>
<th>Type of Studies</th>
<th>Subjects</th>
<th>Results/Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wahlbeck et al, 1999</td>
<td>Meta-analysis</td>
<td>Clozapine vs. FGA: 30 studies</td>
<td>2530</td>
<td>Patients treated with clozapine showed more clinical improvement (NNT=3) and less relapses (NNT=6) in long term than in short term studies (NNT=20)</td>
<td></td>
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<tr>
<td>Taylor and Duncan, 2000</td>
<td>Systematic Review</td>
<td>Clozapine: 8 studies vs. FGA Risperidone: 4 studies (2 vs. Haldol and 2 vs. Clozapine)</td>
<td>1864</td>
<td>Clozapine is effective in TRS Data on other SGAs are inconclusive</td>
<td></td>
</tr>
<tr>
<td>Moncrieff, 2003</td>
<td>Systematic review and meta-analysis</td>
<td>Clozapine vs. FGA: 9 studies</td>
<td>1199</td>
<td>High heterogeneity of studies. Meta-analysis using ITT showed a range of 0.38(FEM) to 0.44 SDs(REM) favoring clozapine</td>
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</table>

Pragmatic Trials:

- Designed to measure effectiveness in real world setting.
- Evoy and colleagues in phase II trial in the Clinical Antipsychotic Trials of Intervention Effectiveness Study (which involved 1400 patients), studied 99 patients who had not responded to atypical antipsychotics in previous phases of trial because of lack of efficacy.
- Patients were assigned randomly to open label clozapine (n=49) or to blinded treatment with another SGA (olanzapine, n=15, quetiapine, n=15, or risperidone n=16). When compared with other SGAs, clozapine had the greatest reductions in the PANNS total score and the lowest discontinuation rates.
- Use of clozapine proved to be more effective than switching to another SGA in patients who previously had not responded to another SGA.
Suicide

- The 2 year International Suicide Prevention Trial in which 980 patients who had schizophrenia (260 had TRS), recruited from 67 medical centers in 11 countries, were assigned randomly to olanzapine or clozapine.
- The rates of suicidal behavior or suicide attempts were significantly lower in patients taking clozapine than those taking olanzapine.
- The rates of deaths from suicide were not statistically significant different between groups.

Predictors of Clozapine Response:

- High psychopathological levels, female gender and years of schooling are predictors of good response.
- Doses of clozapine of 300 to 600mg/d correlate with the plasma threshold for response.
- Although studies are not unanimous, plasmatic levels ≥ 350ng/ml and reaching 500ng/ml tend to be associated with good response when not influenced by the use of nicotine.
- Genetic variants caused by polymorphisms of the dopaminergic receptors D2, D3 and D4 and genetic variants of the serotoninergic receptors 5HT2a, 5HT2c and 5HT6 have been shown to influence the response.

Neuroimaging Factors for Response to Clozapine

Structural Factors

- The prefrontal region has an important role in the mediation of treatment response to atypical antipsychotics.
- 3 CT studies found that an increased prefrontal sulcal prominence was associated with lesser response to clozapine (Friedman et al, 1991).
- An MRI study found that larger right prefrontal gray matter volumes were associated with better treatment response in patients taking clozapine, as compared with those treated with haloperidol (Arango et al, 2003).

Functional factors

- Studies using PET and SPECT have observed an association between a reduction of metabolic activity in the prefrontal regions and clozapine response.
- Studies using PET found reduced metabolic rates in the frontal lobes and increased metabolism in the striatum.
- Chen and colleagues showed opposite results i.e. increased prefrontal activity associated with clozapine response.
- Chung and Remington suggested there are no predictors of treatment response and rather called them markers.
Is there a rationale for antipsychotic polypharmacy?

- Reasons clinicians may use SGA polypharmacy in patients with schizophrenia include the following:
  1. To enhance dopamine (D2) receptor blockade
  2. To achieve antagonism of multiple receptors
  3. To achieve agonism at certain receptors
  4. To optimize pharmacokinetic effects

Reviews of SGA Polypharmacy:

- In 2002, Freudenreich and Goff reviewed 12 reports concerning 147 patients receiving combinations of SGAs or an SGA plus an FGA.
  - The authors concluded that use of antipsychotic polypharmacy is "currently unsupported" and that more trials are needed.
- In 2004, Lerner et al reviewed data from 201 cases of patients with treatment resistant schizophrenia or schizoaffective disorder treated with combinations of SGAs.
  - They discussed 19 case reports, 2 abstracts from open label trials, 1 double blinded placebo controlled trial of 28 patients receiving clozapine plus sulpiride.
  - Lerner et al in 2004 concluded that combinations of SGAs were well tolerated and may be effective in managing treatment refractory schizophrenia and schizoaffective disorder, but more double blinded placebo controlled trials are needed.
  - Patrick et al, 2005 systematically assessed efficacy of combination versus monotherapy with any antipsychotic.
  - The most frequent combination - clozapine plus risperidone.
  - Patrick et al, concluded that the clinical practice of antipsychotic polypharmacy is currently not evidence based but that there is no evidence against its use and recommended further systematic research.

Combinations with Clozapine

- Clozapine Plus Risperidone:
  - Elkis et al identified 26 reports concerning clozapine plus risperidone most of which involved adding risperidone in patients taking clozapine of which 4 were RCTs.
  - Josiassen et al evaluated clozapine plus risperidone in a randomized double blind placebo controlled trial involving 40 pts with schizophrenia/ schizoaffective disorder.
  - The clozapine(mean dose 528.6± 166.7mg/d)-risperidone(1-6mg/d) group showed a statistically significant faster reduction in BPRS positive symptom subscale scores than the clozapine-placebo group.
Combinations with Clozapine

- Clozapine plus Sulpiride or Amisulpiride:
  - One double blind, placebo controlled trial, one single blind randomized trial and five cases were identified that involved use of a combination of clozapine plus sulpiride or amisulpiride.
  - Agelink et al reported a significant decrease in mean BPRS and CGI scores in 6/7 patients in whom amisulpiride (average dose 543mg/day) was added after a mean of 30 weeks clozapine monotherapy (average dose 293mg/day).

Other combinations involving Clozapine

- No RCTs involving combinations of clozapine and other SGAs have been published.
- Currently there does not appear to be sufficient evidence to recommend use of SGA polypharmacy as a routine intervention to improve positive and negative symptom response, even as the fourth or fifth step in treatment algorithm for acute or chronic schizophrenia (Pandurangi et al, 2008).
- The Cochrane Collaboration in 2009 concluded that although clinical guidelines recommend a second antipsychotic in addition to clozapine in partially responsive patients with schizophrenia (NICE 2002), people with clozapine resistant schizophrenia should consider that no particular combination strategy has been shown superior to others.

Other augmentation strategies:

- There are numerous reports available addressing augmentation strategies in patients who are partial responders to clozapine.
- Published reports of controlled double blind studies of augmentation strategies in non responders to clozapine include augmentation with
  - Antidepressants: fluoxetine, mirtazapine
  - Antipsychotics: sulpiride, risperidone
  - Mood stabilizers: lithium, lamotrigine
  - Glutamatergic agents: Glycine, serine, cycloserine

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Augment agent</th>
<th>Dose mg/day</th>
<th>Trial Dur weeks</th>
<th>Efficacy</th>
<th>Sig. adv. events</th>
</tr>
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<tbody>
<tr>
<td>Antidepressants</td>
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<tr>
<td>Buchanan et al</td>
<td>33</td>
<td>Fluoxetine</td>
<td>48.9</td>
<td>8</td>
<td>BPRS,SANS,HDRS: No improvement</td>
<td>None</td>
</tr>
<tr>
<td>Zocalli et al</td>
<td>24</td>
<td>Mirtazapine</td>
<td>30</td>
<td>8</td>
<td>Improvement in BPRS &amp; SANS total scores</td>
<td>None</td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Small et al</td>
<td>20</td>
<td>Lithium</td>
<td>Target to 0.5mmol/L</td>
<td>4</td>
<td>PANSS,CGI improvement in schizoaffective, no improvement in schizophrenia</td>
<td>Rev. neurotoxic reactions (n=2)</td>
</tr>
<tr>
<td>Tiilamo et al</td>
<td>34</td>
<td>Lamotrigine</td>
<td>200</td>
<td>14</td>
<td>PANSS posi and gen psychopathol scores: improvement. PANSS (neg and total) no improvement</td>
<td>none</td>
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Augmentation of clozapine partial responders: double blind studies
Augmentation of clozapine partial responders: double blind studies

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<tr>
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<th>Dose</th>
<th>Trial Durat. wks</th>
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<tr>
<td>Glutamatergic agents</td>
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<tr>
<td>Goff et al</td>
<td>17</td>
<td>Cycloserine</td>
<td>50</td>
<td>6</td>
<td>SANS, PANSS (neg score): worsening</td>
<td>None</td>
</tr>
<tr>
<td>Tsai et al</td>
<td>20</td>
<td>Serine</td>
<td>30mg/kg</td>
<td>6</td>
<td>PANSS, SANS, CGI: No improvement</td>
<td>None</td>
</tr>
<tr>
<td>Potkin et al</td>
<td>19</td>
<td>Glycine</td>
<td>30g/d</td>
<td>12</td>
<td>BPRS, SANS: No improvement</td>
<td>None</td>
</tr>
</tbody>
</table>

Nonpharmacologic augmentation strategies

- Role of ECT:
  - Tang and Ungvari compared a group of 15 patients who had TRS (some where resistant to clozapine) with 15 controls (who had refused clozapine or had switched to another antipsychotic medication).
  - After certain number of sessions, the investigators observed improvement in outcome measures such as CGI score but not in psychopathological measures such as BPRS.
  - In an open label study ECT was administered to 11 clozapine non responders who showed improvement in positive and negative symptoms and in global score on the PANSS (Kho et al).
  - The eight who responded were followed for a mean period of sixteen weeks and four of them relapsed (Kho et al).

Nonpharmacological augmentation strategies contd.

- Role of TMS
  - rTMS (repetitive transcranial magnetic stimulation) was developed and investigated over the last 10 years
  - Most extensive literature focuses on use of low frequency stimulation to attempt to disrupt or reduce the intensity of persistent refractory AH when applied to temperoparietal cortical region
  - Prefrontal rTMS has promise but requires further evaluation in Rx of neg. sx of schizophrenia

Nonpharmacological augmentation strategies contd.

- Psychosocial strategies:
  - CBT has been used extensively in patients who are refractory to antipsychotic medications.
  - Review by Rathod et al, 2008 concluded that CBT has emerged as an effective adjuvant to antipsychotic medication in the treatment of persistent psychotic symptoms of schizophrenia
  - Principal aim of CBT for persistent psychotic symptoms is to work collaboratively with patient to facilitate improved understanding and coping to reduce suffering and improve functioning
Take home points

- TRS continues to be a challenge for clinicians despite considerable progress in the therapeutics of schizophrenia.
- Neurobiological mechanisms underlying TRS are still unclear and progress will come through adequately powered RCTs.
- SGAs should be used as the first two steps for treatment of psychotic episodes of schizophrenia.
- Presently available evidence from RCTs, practical trials, meta-analyses, guidelines and algorithms indicates clozapine is the third step.
- Current augmentation strategies are essentially empiric and based on case reports or open trials without enough evidence.
- Urgent need for intense research, particularly well designed RCTs.

Thank you!

Questions?