The Prospective Incidence of Treatment Resistant Schizophrenia: Analysis of the CATIE Trial using the TRRIP Consensus

Supplementary Information

1. Methods and Algorithms: TRRIP Implementation

1.1 Current Symptoms and Response

Before percentage changes were computed, the PANSS item scores were adjusted so that 0 represents an absence of symptoms, and consequently, 6 represents the most severe rating on any of the 30 items. This concords with the methods described in [1] and advocated in the TRRIP consensus for measuring symptom changes / response.

1.2 Social and Occupational Function

The TRRIP consensus recommends using a validated scale such as the SOFAS, and sets the threshold for "moderate impairment" as a score of less than 60 on the 0-100 scale. The original SOFAS provides an unstructured and linguistically vague set of descriptors [2] whereas their Personal and Social Performance (PSP) scale provides an operationalised version with four domains: (A) socially useful activities, including work and study, (B) personal and social relationships, (C) self-care, and (D) disturbing and aggressive behaviours

The equivalent of moderate impairment (on the SOFAS or Global Assessment of Function scale) using the PSP [2] is defined as "Marked [difficulties] in 1 of general areas A-C, or manifest difficulties in D" which equates to a global assessment of functioning score of 51-60.

In the CATIE trial, there are three instruments which cover social and occupational functioning:

1. clinician-rated social functioning and interpersonal relationships are measured by the Heinrichs-Carpenter Quality of Life Scale (QLS) [3]
2. the Lehman Quality of Life Interview (QOLI) measures physical, economic, social, and psychological functioning, employment, leisure, and residence [4]
3. the MacArthur Community Violence Instrument [5] is used to estimate risk of violence and aggression.

From these three instruments, we produced a proxy PSP score as follows:

(A) socially useful activities, including work and study was measured by taking the "instrumental role" score on the Heinrichs-Carpenter QLS. A score of between 5-6 indicates "excellent / little impairment", with a threshold of less than or equal to 3 indicating moderate impairment and 0-1 being severe impairment [3].

(B) personal and social relationships is equated with "interpersonal relations" score in the Heinrichs-Carpenter QLS, with the same scoring as "instrumental role" above

(C) self-care is sub-divided into three domains, extracted from the QOLI and QLS:

(1) **accommodation status** where a maximum score of 5 indicates fully independent living, with the moderate impairment threshold at 3 "moderately supported accommodation", 2 being "extremely restricted accommodation" and 1 equating to homelessness)

(2) **activities of daily living related to self-care** defined with 4 being the highest level (wash, do laundry, clean room, do chores) and a moderate threshold of 3 meaning professional help is required with at least one of these activities, and 0 being unable to do any of these tasks without help

(3) **independence** scored as 1 point for each of: reminding for a) appointments or b) to take medication and requiring supervision c) to take the participant to appointments or d) take medication – a score of 4 indicates complete independence, and a threshold of 3 was used for moderate impairment (i.e. at least one activity requires reminders with another requiring direct supervision).

The overall self-care (C) domain score is calculated to be at or below the "moderate impairment" threshold with a score of less than or equal to 3 in either (2) activities of daily living / (3) independence *or* less than or equal to 3 on (1) accommodation status, because living in moderately supported accommodation implies moderate impairment on the PSP [2] where they define "marked impairment" as "the person is still able to do something without professional or social help, although inadequately and/or occasionally; if helped by someone, he/she may be able to reach the previous level of functioning".

(D) disturbing and aggressive behaviours are defined in the PSP [2] as *severe* by "frequent verbal threats or frequent physical assaults, without intention or possibility to severe injuries" and suggests downgrading to "marked" impairment if occasional (rather than frequent) which is operationalised as less than 3 occurrences in a time period. We produced a proxy measure using the MacArthur scale by considering only items measuring aggression or violence directed at others by summing scores of 0 (did not occur) or 1 (did occur) over activities 1) throwing an object at someone, 2) pushed/grabbed/shoved someone, 3) slapped someone, 4) kicked/bitten/choked someone, 5) hit someone with fist/object or beaten up someone, 6) attempt to force someone to have sex, 7) threatened someone with gun/knife, 8) used knife/fired a gun on someone, 9) anything else considered violent, and 10) physically hurt someone – bruise, cut, broken bone, knocked unconscious – irrespective of mechanism). This yields

a total score between 0-10. Given that *any* of these individual descriptors on the MacArthur scale would certainly meet the criteria for "severe" or "marked" impairment on the PSP, we set a threshold of greater than or equal to 3 (by Morosini et al. (2000)'s definition of occasional) as being "marked" for the disturbing and aggressive behaviour domain in our proxy PSP measure.

After calculating the individual proxy domains (A) through (D) using the above rubric, we then set the overall SOF score to meet threshold for moderate impairment (i.e. meeting the TRRIP consensus for treatment resistance threshold on SOF) using the above rule: if the participant demonstrates "marked" impairment in one of A through C, or manifest difficulty in D. This equates to an overall 0-100 scaled score (e.g. for comparison with the SOFAS scale) of 51-60 and similarly, equates to a Global Assessment of Function (GAF) score indicating "moderate impairment" [2] . Of note, our rule for (D) cannot distinguish between "marked" and "manifest" (the lower rating) so it is likely our proxy SOFAS/PSP measure underestimates impairment on this domain, because only the more aggressive/violent (rather than disturbed) behaviours are captured. For missing data items, we assumed *no* impairment so again, our proxy for SOFAS is likely underestimating, rather than exaggerating, impairment in social and occupational functioning.

1.3 Adequate Treatment

We sourced summary-of-product characteristics (SPCs) for each antipsychotic:

- Ziprasidone http://labeling.pfizer.com/ShowLabeling.aspx?id=584
- Olanzapine http://pi.lilly.com/us/zyprexa-pi.pdf
- Risperidone:http://www.janssen.com/us/sites/www_janssen_com_usa/files/products-documents/risperdal-prescribing-information.pdf
- Perphenazine https://www.medicines.org.uk/emc/medicine/22596

- Quetiapine https://www.medicines.org.uk/emc/medicine/2295
- Aripiprazole https://www.accessdata.fda.gov/drugsatfda_docs/label/
- 2014/021436s038,021713s030,021729s022,021866s023lbl.pdf
- Clozapine https://www.medicines.org.uk/emc/medicine/32564
- Fluphenazine long acting injectible/depot http://www.medicines.org.uk/emc/medicine/6956/SPC/Modecate+Injection+25mg+ml

Table S1: Dose Thresholds for Adequate Treatment Trials

	SPC Recommended Dose Range		
Medication	Minimum (mg)	Maximum (mg)	Midpoint Threshold (mg)
Ziprasidone	40	200	120
Olanzapine	10	15	12.5
Risperidone	4	16	10
Perphenazine	12	24	18
Quetiapine	150	750	450
Aripiprazole	10	30	20
Clozapine	200	450	325
Fluphenazine	12.5	100	56.25

The minimum adequate dose thresholds used are given in Table S1 and were determined as the mid-point between the minimum and maximum doses given in each medication's SPC as: minimum dose + (maximum dose – minimum dose)/2.

Only treatment episodes where the dose was greater than or equal to the midpoint were included as adequate treatment episodes.

1.4 Event Model

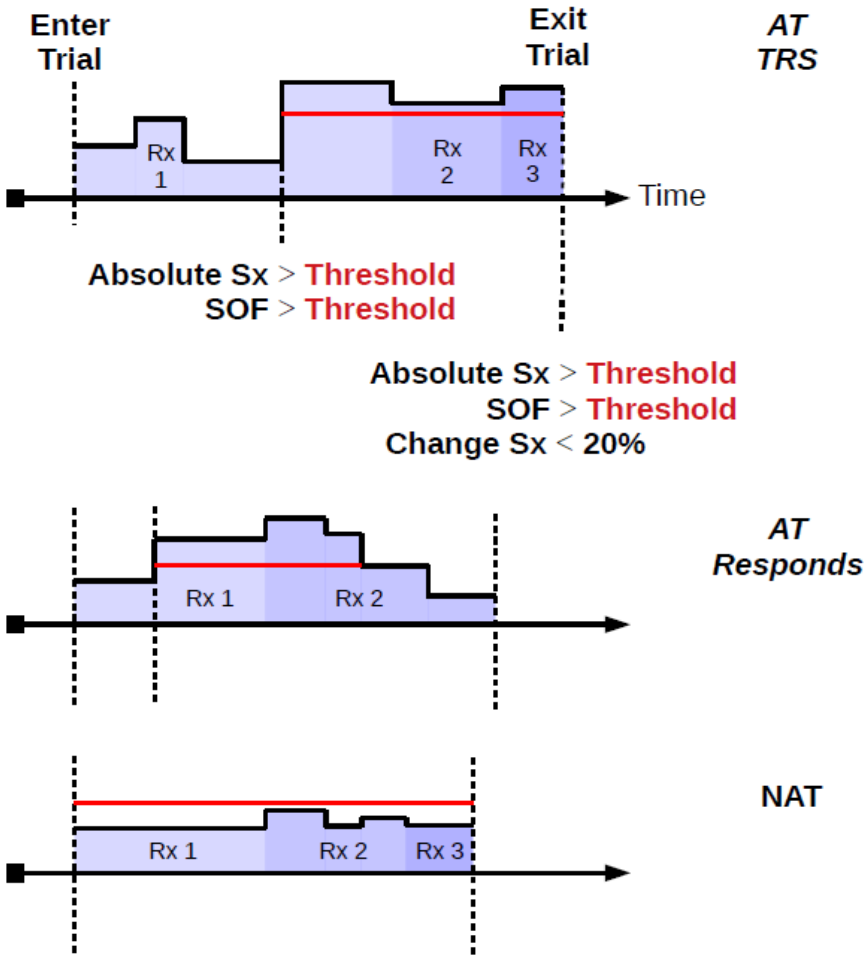

Figure S1: Event Model for Operationalized TRRIP; Example participant trajectories are **Top Panel** meets the absolute criteria threshold, has 2 or more adequate treatments and whose response is less than 20%; **Middle Panel** meets the absolute criteria threshold, but responds to treatment; **Bottom Panel** never reaches the absolute criteria. AT = above threshold, NAT = never above threshold.

References

1. Leucht S, Davis JM, Engel RR, Kissling W, Kane JM. Definitions of response and remission in schizophrenia: recommendations for their use and their presentation. *Acta Psychiatr Scand Suppl.* 2009(438):7-14.
2. Morosini PL, Magliano L, Brambilla L, Ugolini S, Pioli R. Development, reliability and acceptability of a new version of the DSM-IV Social and Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning. *Acta Psychiatr Scand.* 2000;101(4):323-329.
3. Heinrichs DW, Hanlon TE, Carpenter WT, Jr. The Quality of Life Scale: an instrument for rating the schizophrenic deficit syndrome. *Schizophr Bull.* 1984;10(3):388-398.
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