The use of defined inclusion criteria to establish baseline cognitive deficits in CIAS clinical trials

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Background

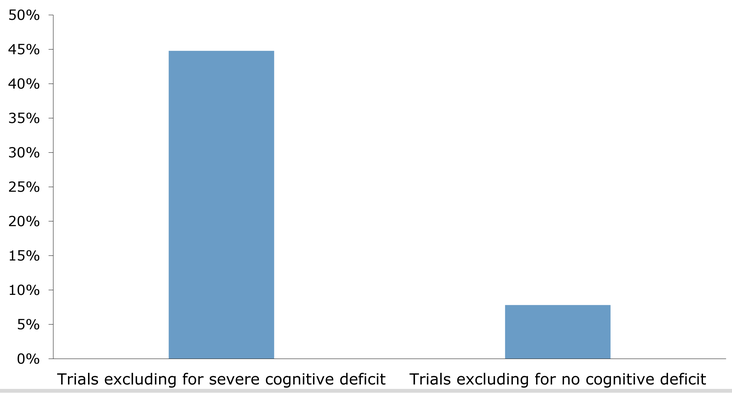
- Cognitive deficits are a core feature of schizophrenia but not all patients function below the normal range expected in the absence of illness[1,2]
- Although 98% of patients with schizophrenia may qualify as cognitively impaired compared to antecedent expectations such as premorbid intelligence[3], some patients will still not meet neuropsychological criteria for clinically relevant impairment
- For a positive signal to be detected in a clinical trial, below normal performance must be obtained in the key neuropsychological tests at screening/baseline
- The aim of the current research was to establish the extent to which subjects are pre-screened for cognitive deficits in clinical trials using cognition as an endpoint

Methods

- Systematic searches were carried out on www.ClinicalTrials.gov for all protocols associated with schizophrenia from 2000 to December 2016 (N = 614). Trial registration on this trial registry started in 2000 for NIMH grants and in 2002 for industry-sponsored trials
- Information was collated on primary and secondary study objectives, use of active intervention, cognitive endpoints, baseline cognitive impairment as an inclusion criterion and its definition (where applicable), other quantitative/qualitative inclusion and exclusion criteria, NCT trial registration number and sponsor

Establishing Baseline Cognitive Deficits is Uncommon

- Out of the 614 studies that used cognition as an endpoint, only 48 (7.8%) employed inclusion or exclusion criteria to establish the presence of a cognitive deficit
- This can be compared with 44.8% of the 614 clinical trials that employed inclusion or exclusion criteria to eliminate subjects who demonstrate severe cognitive deficits



CIAS Trials with Cognition as a Primary Endpoint are More Likely to Establish Baseline Deficits

Trials Excluding for Severe Cognitive Deficit

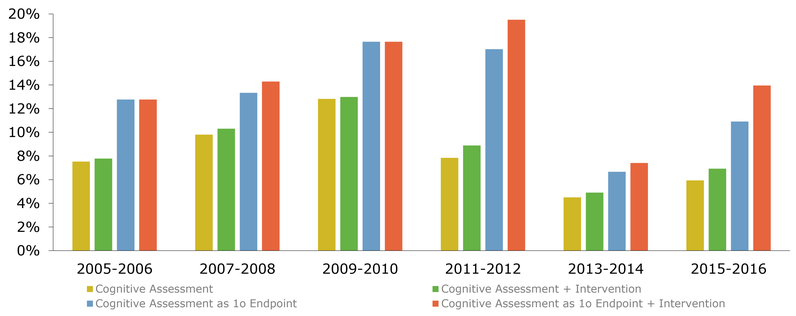
	Cognitive Assessment	Cognitive Assessment + Intervention	Cognitive Assessment as Primary Endpoint	Cognitive Assessment as Primary Endpoint + Intervention
All trials	275/614 (45%)	256/567 (45%)	170/326 (52%)	157/298 (53%)
Academic	239/489 (49%)	220/445 (49%)	152/270 (56%)	140/244 (57%)
Commercial	36/125 (29%)	36/122 (30%)	18/56 (32%)	18/54 (33%)
Cold Cognition Only*	235/541 (43%)	221/504 (44%)	141/278 (51%)	132/256 (52%)
Hot Cognition Only*	15/25 (60%)	11/20 (55%)	12/20 (60%)	8/15 (53%)

Trials Excluding for No Cognitive Deficit

	Cognitive Assessment	Cognitive Assessment + Intervention	Cognitive Assessment as Primary Endpoint	Cognitive Assessment as Primary Endpoint + Intervention
All trials	48/614 (8%)	48/567 (8%)	42/326 (13%)	42/298 (14%)
Academic	38/489 (8%)	38/445 (9%)	35/270 (13%)	35/244 (14%)
Commercial	10/125 (8%)	10/122 (8%)	7/56 (13%)	7/54 (13%)
Cold Cognition Only*	40/541 (7%)	40/504 (8%)	35/278 (13%)	35/256 (14%)
Hot Cognition Only*	2/25 (8%)	2/20 (10%)	2/20 (10%)	2/15 (13%)

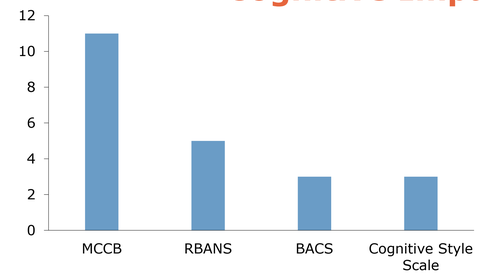
*Cold cognition – emotion independent
*Hot cognition – emotion laden

Percentage of Trials Excluding for No Cognitive impairment by Year



- Until the FDA-NIMH-MATRICs Workshop in 2005, there were <10 CIAS trials that excluded participants with no cognitive impairment
- 2013-2014 witnessed a decline in the proportion of CIAS trials screening for cognitive impairment

Common Assessments used to Exclude for No Cognitive Impairment



Other assessment include:

- CVLT
- Stroop
- CPT
- HVLT
- VSWM
- WCST
- Oculomotor Delayed Response Task
- Intention Reading
- Reading the Mind in the Eyes
- Cognitive Empathy Assessment

- 9/11 MCCB CIAS trials, used MCCB to screen for cognitive deficits and as the cognitive endpoint.

Conclusions

- A minority of studies using cognitive endpoints in schizophrenia clinical trials from 2000-2016 used inclusion criteria to ensure cognitive deficits existed at baseline
- In contrast, a substantial number excluded participants with severe cognitive deficits
- Whilst it is important to ensure exclusion of patients with major impairments, it should be equally important to ensure inclusion of patients with at least minimal but clinically relevant impairment, as this may increase the chance of seeing an improvement in cognitive performance in the trial
- Whilst patients 'within the normal range' by clinical neuropsychological criteria may benefit from a pharmacologic intervention in clinical practice (if they are impaired compared to their premorbid level of function), their inclusion in clinical trials will inflate baseline scores, increase the risk of ceiling effects and minimise chance to see change
- This can be overcome by screening in participants with a quantitative cognitive deficit using tests with clear, established norms or an absolute scale
- Regulatory bodies IRBs and grant funding agencies should be aware of the potential impact of including subjects with no cognitive impairment, and preferably require quantitative assessments of cognition as a condition for protocol approval
- Take home message: To see an improvement in cognitive performance, there must be a quantifiable cognitive deficit at baseline.

Limitations

- Limited to protocols published in clinicaltrials.gov
- Not all inclusion and exclusion criteria are listed in the protocol
- Not all exploratory outcome measures are listed in the protocol (For example: Can confirm that CANTAB has been included in some protocols, but not listed in clinicaltrials.gov)
- Some researchers (academic and commercial) register trials retrospectively (i.e. received date is several years after start date)

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