



Correspondence

Insights from pre-treatment attrition & dropouts in an effectiveness trial of methylphenidate in children

Sir,

Methylphenidate is a first-line drug for attention-deficit/hyperactivity disorder (ADHD)¹. Drug discontinuation is extremely common particularly in children with ADHD^{2,3}; and is associated with worse clinical outcomes³. In addition, pre-treatment attrition leads to undertreatment⁴. Common reasons for attrition include adverse effects, inadequate symptom control, dosing inconvenience, social stigma and patient's/caregiver's attitude^{2,3,5-8}. Sociocultural reasons for non-adherence are unique to different settings⁵⁻⁸ and are clinically relevant. The objectives of this correspondence were to report pre-treatment attrition and dropout rates for methylphenidate in children with ADHD and reasons and correlates for the same in our setting.

The study was conducted in the Child and Adolescent Psychiatry services of the department of Psychiatry, Postgraduate Institute of Medical Education & Research (PGIMER), Chandigarh, India, from 2015 to 2017. Ethical clearance was obtained from the Institutional Ethical Committee prior to intake. Children aged 6-15 yr with the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV-TR)⁹ diagnosis of ADHD confirmed by the Mini International Neuropsychiatric Interview-KID¹⁰, with or without ID [intelligence quotient (IQ) as measured by the Malin's Intelligence Scale for Indian Children¹¹ and/or Vineland Social Maturity Scale-Indian Adaptation <70]¹², and were either drug naïve or off medications for the last three months, were recruited. As the study had an effectiveness design, children with common comorbid behavioural and neurodevelopmental conditions, namely, oppositional defiant/conduct disorder (ODD/CD), specific learning disorders (SLD) and autism spectrum disorder (ASD) were also included. Those with other comorbid

psychiatric illness, history of epilepsy, cardiac disease, exercise intolerance/syncope, tics, sensitivity to stimulants or young sudden cardiac death in family were excluded. All parents and children (to extent possible) were informed in detail about the different pharmacological and non-pharmacological alternatives for treatment. Written informed consent and assent (wherever possible) were obtained from parents and children, respectively. Assuming alpha=0.05 and power=0.80, for 30 per cent response in primary outcome measure, a sample size of 30 was needed for each group in the before-after study.

Immediate-release methylphenidate was prescribed at the starting doses of 0.15-0.3 mg/kg, which was increased to 0.3 mg/kg after one week (2.5-5 mg/dose in single morning dose) as used by others⁶. Optimal dose titration as indicated by improvement and side effects was planned at weeks 2-4, 6-8, 10-12 and 16-20 to reach, if needed, a maximal optimal dose of 1.2 mg/kg. Participants who visited directly for the 6th-8th week follow up visit after baseline were considered to have their first follow up and dose titration was done as indicated at the first follow up and so on for other follow up points. Non-drug management was continued as usual. No other ADHD drug was given. Baseline and follow up assessments for the primary outcome measure of symptom severity were carried out by an independent interviewer using Vanderbilt ADHD Diagnostic Parent Rating Scale (VADPRS)¹³. Telephonic or in-person interviews were conducted with parents and children (n=8) who did not start methylphenidate post-recruitment (pre-treatment attrition) and dropped out after initiation of the drug to elicit the reasons for attrition and dropout. Starters and non-starters (pre-treatment attrition), completers and non-completers and continuers and discontinuers of medication (among those who started) were compared

on demographic and clinical variables using Student's *t* test/Mann-Whitney U-test or Fisher's exact test. Those with and without ID were compared using the Fisher's exact test.

Seventy six children were screened; 49 children fulfilling the selection criteria were approached and finally 35 consenting participants were included. Among non-consenting ones, parents/family preferred an initial trial of behavioural management (n=10), needed to discuss with other family members regarding medication (n=5), preferred another ADHD medication (n=2) and were not convinced about the need for treatment (n=2). The mean age of participating children was 10.3±2.75 yr, and majority were males (88.6%). Baseline VADPRS (items 1-18) scores were 58.83±14.89. Thirty two (91.4%) children had combined type of ADHD. Eight (22.9%) had ID. There was no difference between those with ID and those without in terms of age, gender, the family type or monthly family income, while baseline VADPRS scores were significantly greater in those with ID ($P<0.01$). Overall, six children had ODD/CD, three had ASD and two had SLD.

Twenty seven (7 with ID and 20 without ID) of the 35 children started methylphenidate, resulting in pre-treatment attrition of 22.86 per cent. Pre-treatment attrition in those with ID (12.5%) and without ID (25.9%) did not differ significantly. Those who belonged to joint families were more likely not to start medication as compared to those who belonged to nuclear families (43.75 vs. 5.26%, $P<0.01$). Non-starters did not differ from those who started medication on age, gender, IQ, baseline symptom severity, presence of comorbidity and family income. The Table depicts the comparison between those who started the medication with those who did not.

Post-recruitment, dropout rates (n=35) at the four follow up points were 37.1, 42.9, 48.6 and 57.1 per cent, respectively. Sequential dropout rates were 37.1, 9.1, 10 and 16.7 per cent. Cumulative attrition rates for those who started methylphenidate (n=27) were 18.5, 25.9, 33 and 44.4 per cent at the first, second, third and fourth follow up points, respectively. One child did not adhere to the study protocol and was considered as a discontinuer. Among those who started methylphenidate, those with ID were more likely to discontinue the drug at all the follow up points (1st: $P<0.01$, 2nd: $P<0.05$, 3rd: $P<0.05$ and 4th: $P<0.05$). Symptom severity (VADPRS items 1-18 total

score) at the last observation was significantly higher ($P<0.01$) in those with ID (n=7) as compared to non-ID (n=20). Mean change in scores from baseline to the last observation was significant ($P<0.001$) in both the groups (with and without ID) and was not different between the two groups. Severe side effects were significantly higher ($P<0.05$) in discontinuers (33.33%) as compared to continuers (0%). Severe side effects were more often present in those with ASD ($P<0.05$), but not ID. Severe side effects included seizure, severe irritability/agitation and severe loss of appetite with significant weight loss.

Qualitative interviews (n=19) were carried out in person in nine and telephonically in 10 cases. One family could not be contacted from pre-treatment attrition group. In pre-treatment attrition group (n=7), multiple reasons were stated, namely, either parents/family member(s) was uncomfortable with diagnosis, concerned about medication side effects or were unsure about the need for medication and treatment expenditure. Reasons for post-treatment attrition (n=12) included expenses towards medication and hospital visits (n=5), side effects (n=4), parental perceptions regarding the need for pharmacotherapy and concern about appetite suppression (n=2), non-adherence to the study protocol (n=1), inadequate improvement (n=1) and preference of the child (n=1).

In our study, about a quarter did not initiate methylphenidate and almost half of those who started discontinued. Studies from India reported discontinuation rates of 62.5 to 83.3 per cent^{6,7}. Decisions and reasons for attrition may be associated with treatment-related and sociocultural factors^{3,5-8}. Our findings suggested that not only parental, but also family perceptions and preferences regarding the need for medication and concerns about side effects were important reasons for both pre-treatment attrition and drug discontinuation. Similar parental fears have been reported from India⁶ and elsewhere⁵. Earlier studies have also shown that often other family members discourage the use of drug^{6,7}, and that family pressures to avoid medication is an important barrier to drug initiation⁵. In the light of these and our findings, involvement of other close family members for treatment decision-making may be considered as crucial and culturally relevant¹⁴. Another reason cited was the cost of drug and overall treatment. In India, methylphenidate is an expensive drug and treatment expenses including medication and hospital visits are fully borne by the families⁶.

Table. Comparison between starters and non-starters of medication (pre-treatment attrition) and between those who discontinued and continued the medication

Parameters	Pre-treatment attrition (n=35)	
	Mean±SD/frequency	
	Non-starters (n=8)	Starters (n=27)
Age (yr)	9.62±3.58	10.29±3.75
Gender (male), n (%)	8 (100)	23 (85.2)
IQ	92.12±13.26	81.89±19.61
Presence of ID	1 (12.5)	7 (26)
Baseline symptom severity	35.16±7.18	38.07±9.15
Presence of comorbidity	1 (12.5)	10 (37.03)
Family type (joint)	7 (87.5)	9 (33.34)**
Parameters	Discontinuation among those who started medication (n=27)	
	Mean±SD/frequency	
	Discontinuers (n=12)	Continuers (at the end of study) (n=15)
Age (yr)	10.00±2.92	10.53±2.69
Gender (male), n (%)	10 (83.34)	13 (86.67)
IQ	74.92±19.13	87.60±18.60
Presence of ID	6 (50)	1 (6.67)*
Baseline symptom severity	36.42±8.13	39.40±9.97
Presence of comorbidity	4 (33.34)	6 (40)
Presence of ASD	3 (25)	0 (0)
Presence of severe side effects	4 (33.34)	0 (0)*
Family type (joint)	4 (33.34)	5 (33.34)

Values in parentheses are percentages. $P^* < 0.05$, $** < 0.01$ compared to respective group. ID, intellectual disability; IQ, intellectual quotient; ASD, autism spectrum disorder

Adverse effects and treatment ineffectiveness have been frequently reported as reasons for discontinuation³. In our study, severe side effects were associated with drug discontinuation and were observed more in those with ASD. Although there is growing evidence for methylphenidate as first-line ADHD drug even in those with ASD¹, our study findings indicate caution and close monitoring. Drug discontinuation was higher in those with ID, though there was no evidence for decreased effectiveness or increased severe side effects as compared to non-ID children on preliminary analysis.

This study had some major limitations. Sample size of the subgroups was small and unequal, limiting the power to study group differences. Thus, findings should be interpreted cautiously. Our findings may not be generalized to other psychopharmacological agents or patient groups. Further, telephonic interviews may

also have limited the reliability of our findings. To conclude, parental perceptions, comorbidities and drug side effects may play an important role in pre-treatment attrition and dropout.

Financial support & sponsorship: Authors acknowledge the PGIMER, Chandigarh, for providing financial support to this study.

Conflicts of Interest: None.

Ruchita Shah*, Susanta Padhy, Adarsh Kohli & Samita Sharma

Department of Psychiatry, Postgraduate Institute of Medical Education & Research, Chandigarh 160 012, India

*For correspondence:
e-mail: druchitashah@gmail.com

Received August 10, 2018

References

1. National Institute for Health and Care Excellence. *Attention deficit hyperactivity disorder: Diagnosis and management*. London: National Institute for Health and Care Excellence; 2018.
2. Adler LD, Nierenberg AA. Review of medication adherence in children and adults with ADHD. *Postgrad Med* 2010; *122* : 184-91.
3. Gajria K, Lu M, Sikirica V, Greven P, Zhong Y, Qin P, *et al*. Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder - a systematic literature review. *Neuropsychiatr Dis Treat* 2014; *10* : 1543-69.
4. Victor MM, Grevet EH, Salgado CA, Silva KL, Sousa NO, Karam RG, *et al*. Reasons for pretreatment attrition and dropout from methylphenidate in adults with attention-deficit/hyperactivity disorder: The role of comorbidities. *J Clin Psychopharmacol* 2009; *29* : 614-6.
5. Coletti DJ, Pappadopulos E, Katsiotas NJ, Berest A, Jensen PS, Kafantaris V. Parent perspectives on the decision to initiate medication treatment of attention-deficit/hyperactivity disorder. *J Child Adolesc Psychopharmacol* 2012; *22* : 226-37.
6. Sitholey P, Agarwal V, Chamoli S. A preliminary study of factors affecting adherence to medication in clinic children with attention-deficit/hyperactivity disorder. *Indian J Psychiatry* 2011; *53* : 41-4.
7. Antony A. Study of factors influencing treatment adherence in childhood attention deficit hyperactivity disorder in a tertiary healthcare facility. *Indian J Psychol Med* 2016; *38* : 20-4.
8. Ahmed R, Borst J, Wei YC, Aslani P. Parents' perspectives about factors influencing adherence to pharmacotherapy for ADHD. *J Atten Disord* 2017; *21* : 91-9.
9. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders: DSM-IV-TR*. Washington, DC: American Psychiatric Association; 2000.
10. Sheehan DV, Sheehan KH, Shytle RD, Janavs J, Bannon Y, Rogers JE, *et al*. Reliability and validity of the mini international neuropsychiatric interview for children and adolescents (MINI-KID). *J Clin Psychiatry* 2010; *71* : 313-26.
11. Malin AJ. Malin's intelligence scale for children. *Indian J Ment Retard* 1971; *4* :15-25.
12. Raj B. Vineland Social Maturity Scale and Manual, Indian Adaptation - Enlarged Version, Swayamsidha-Prakashana, Mya; 1992.
13. Wolraich ML, Lambert W, Doffing MA, Bickman L, Simmons T, Worley K. Psychometric properties of the Vanderbilt ADHD diagnostic parent rating scale in a referred population. *J Pediatr Psychol* 2003; *28* : 559-67.
14. Shah R, Grover S, Avasthi A. Clinical practice guidelines for the assessment and management of attention-deficit/hyperactivity disorder. *Indian J Psychiatry* 2019; *61* : 176-93.