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PSYCHOPHARMACOLOGY

Adverse Effects of Psychotropic Medications in Children: Predictive Factors

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Abstract

Objective: Despite limited information related to efficacy in children, psychotropic medications are commonly prescribed as a first-line treatment for a range of psychiatric diagnoses in children in a variety of clinical settings. Usage has increased over the past three decades. Although psychotropic medications are often effective at treating psychiatric symptoms, the risk of adverse effects (AE) in children is unclear. The current research seeks to identify the mental health characteristics of those children at highest risk of experiencing potential AE from psychotropic medications. **Methods:** Psychotropic medication monitoring checklists were used to record possible AE for 99 pediatric clients in a tertiary mental health residential treatment centre for the duration of one to eight weeks. Client characteristics, including the number of diagnoses and behavioural variables, were explored for predictive value of potential AE observed. **Results:** Results showed that the total number of potential AE was positively predicted by the number of DSM-IV categories diagnosed, as well as behavioural symptoms of impulsiveness and uncooperativeness. **Conclusions:** The findings of this study indicate that the number of potential AE from psychotropic medications may be predictable based on client characteristics. Predicting this likelihood during initial assessment can be useful in directing and monitoring treatment, as well as preventing serious events related to medication use.

***Key Words**: children, adverse effects, psychotropic medication monitoring checklist, residential care*

Résumé

Objectif: Malgré l'information limitée sur leur efficacité chez les enfants, les médicaments psychotropes sont communément prescrits comme traitement de première ligne pour une variété de diagnostics psychiatriques chez les enfants, dans divers milieux cliniques. L'usage a augmenté dans les 30 dernières années. Bien que les médicaments psychotropes soient souvent efficaces pour traiter les symptômes psychiatriques, le risque d'effets indésirables (EI) chez les enfants n'est pas déterminé. La recherche actuelle vise à identifier les caractéristiques de la santé mentale des enfants les plus à risque d'éprouver des EI potentiels des médicaments psychotropes. **Méthodes:** Les listes de surveillance des médicaments psychotropes ont été utilisées pour repérer des EI possibles chez 99 clients pédiatriques dans un centre tertiaire de traitement résidentiel de santé mentale pour une durée d'une à huit semaines. Les caractéristiques des clients, notamment le nombre de diagnostics et de variables comportementales, ont été explorées pour la valeur prédictive des EI potentiels observés. **Résultats:** Les résultats ont indiqué que le nombre total d'EI potentiels était positivement prédit par le nombre de catégories du DSM-IV diagnostiquées, et par les symptômes comportementaux d'impulsivité et de non-coopération. **Conclusions:** Les résultats de cette étude indiquent que le nombre d'EI potentiels des médicaments psychotropes peut être prédictible d'après les caractéristiques des clients. Prédire cette probabilité durant l'évaluation initiale peut être utile pour orienter et surveiller le traitement, et prévenir des incidents sérieux liés à l'utilisation de médicaments.

***Mots clés:** enfants, effets indésirables, liste de surveillance des médicaments psychotropes, soins résidentiels*

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There is much unknown about the use of psychotropic medications and their effects on children. Knowledge of the efficacy, specificity and adverse effects (AE) of psychotropic medications in pediatric populations lags behind what is known in adults (Wolraich, 2003). Despite this, physicians may generalize adult prescribing patterns to children (American Psychiatric Association, 2000). While the benefits of symptom relief often outweigh the risk of AE, determining the risks associated with psychotropic medications is an important endeavour (Bridge et al., 2007).

Children can be more sensitive to AE than adults. In a study of antipsychotic medications, it was found that extrapyramidal AE occur more commonly in young people than adults (Sikich, Hamer, Bashford, Sheitman, & Lieberman, 2004). While second-generation atypical antipsychotics lead to fewer extrapyramidal symptoms, AE associated with these medications include significant weight gain and increased risk of diabetes mellitus and dyslipidemia (Gentile, 2006). AE severity may cause clients or their parents to refuse the continuation of pharmacologic therapy, thereby increasing the risk of re-experiencing their original symptoms (Charach, Volpe, Boydell, & Gearing, 2008).

Despite limited information related to efficacy with children, psychotropic medications are a commonly prescribed first-line treatment for a range of psychiatric diagnoses in children in a variety of clinical settings. Approximately 85% of children diagnosed with attention deficit hyperactivity disorder (ADHD) are prescribed stimulant medications, 60% with bipolar disorder are prescribed mood stabilizers, and 57% of depressed outpatient pediatric clients are treated with antidepressant medications (Moreno et al., 2007; Olfson, Gameroff, Marcus, & Jensen, 2003; Olfson, Gameroff, Marcus, & Waslick, 2003).

The prescribing rate of psychotropic medications is increasing in children, as is the number of medication types prescribed per child (Comer, Olfson, & Mojtabai, 2010; Olfson, Marcus, Weissman, & Jensen, 2002). Over a 12-year period, multiclass psychotropic prescriptions rose in children from 14.3% to 20.2% (Comer et al., 2010). The reasons for these changes may be the increasing level of empirical evidence supporting the usage of psychotropic medications for conditions like ADHD, obsessive-compulsive disorder, major depressive disorder, and childhood anxiety disorders, and a more thorough understanding of the biological basis of these conditions (McClellan & Werry, 2003). Increasing usage of psychotropic medications may also be in response to recent emphasis on rapid symptom reduction by clients, parents, or physicians (Stahl, 2008).

There is further uncertainty as to how children react to being treated with multiclass psychotropic regimens (Safer, Zito, & dosReis, 2003). The risks of AE (including those that are fatal) are potentially compounded by the simultaneous usage of multiple psychotropic medications (Safer et al., 2003), as many potential AE are shared across multiple medication types. A lack of evidence regarding concomitant psychotropic medication administration and its safety has been cited in the past as a concern for children in foster care (Zito et al., 2008). The concern surrounding excessive usage of psychotropic medications has led to the creation of physician training programs and quality improvement initiatives to reduce such prescribing patterns (Patrick, Schleifer, Nurenberg, & Gill, 2006).

Psychotherapy, such as cognitive behavioural therapy (CBT), is also considered a first-line treatment for conditions such as obsessive-compulsive disorder and generalized anxiety disorder (James, James, Cowdrey, Soler, & Choke, 2013). Psychosocial interventions avoid the potential AE of psychotropic medications and are actually preferred by some adolescents over pharmacotherapy (Bradley, McGrath, Brannen, & Bagnell, 2010). However, the costs of psychotherapy in private settings and the lack of such resources in many communities make pharmacotherapy a more readily available option for many (James, Soler, & Weatherall, 2005).

Increasing our knowledge about the efficacy of psychotropic medications and AE in children is vital to ensure client safety. The present study attempts to determine the relationship between the number and commonality/severity of potential AE experienced by children and the number of disorders diagnosed according to criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) and standardized criteria measuring the complexity of psychiatric presentation.

Methods

Ethics approval was obtained from the Western University Research Ethics Board. Consent to use client data for research purposes was obtained from parents/guardians and youth.

Participants

The primary participants were 99 clients (78% boys; M_{age} = 11.97 years; *SD* = 2.35 years) on five residential units at a tertiary mental health care facility for children with complex psychiatric concerns: a short-term stabilization unit for children (ages 6-12 years), a unit for adolescent boys (13-18 years), a unit for adolescent girls (10-18 years), a unit for boys and girls with developmental delays (6-12 years), and a unit for adolescents (13-18 years) with developmental delays. Data collection took place over a four-month time period. These 99 patients altogether provided 565 weeks of data. A secondary pool of 627 clients (77% boys; M_{age} = 12.0 years; *SD* = 2.63 years) from the same residential units over a five-year timespan provided additional data on three standardized instruments at intake to enable scores to be condensed into manageable factors to inform analyses in the current study (see details below).

Materials

The Psychotropic Medication Monitoring Checklists (PMMC; Ninan et al., 2014) were developed over a one-year period by a four-person physician-pharmacist team. The team first identified common psychotropic medications for children, based on the information by the United States Food and Drug Administration (FDA), Health Canada, and the team's consensus opinions. The researchers then proceeded to conduct a comprehensive review regarding potential AE. These sources included product monographs, website resources such as Medscape and the *Clinical Handbook of Psychotropic Drugs for Children and Adolescents* (Bezchlibnyk-Butler & Virani, 2007). Independent AE checklists were prepared for seven classes of prescribed drugs: alpha agonists, anticonvulsants, antipsychotics, atomoxetine, lithium, selective serotonin reuptake inhibitors (SSRIs), and stimulants. Each checklist divides the AE into three categories (common, infrequent, and rare but serious), based on both their likelihood of occurrence and the severity. Observed symptoms are considered "potential" AE rather than "actual" until confirmed by a physician as being directly related to the medication. This step was not included in the design of the current study. An example of the PMMC is provided in Appendix A. Ninan and colleagues (2014) recently demonstrated that the PMMC are useful educational tools that improve AE monitoring by residential staff (i.e., child and youth workers).

The Brief Child and Family Phone Interview (BCFPI; Cunningham, Pettingill, & Boyle, 2004) measures the type and the severity of a child's problems. It includes five mental health subscales (regulating attention, impulsivity, and activity level; cooperativeness; conduct; separating from parents; self-harm), one global functioning scale and one global family situation scale. Its classification reliability has been verified when compared to more extensive diagnostic interviews such as the Diagnostic Interview Schedule for Children- Version IV (Boyle et al., 2008).

The Child and Adolescent Functional Assessment Scale (CAFAS; Hodges, 1994) measures eight problem areas, including school/work, home, community, behaviour towards others, moods/emotions, self-harmful behaviour, substance use, and thinking. Its predictive value for juvenile recidivism, contact with the law, and poor school attendance has been verified (Quist & Matshazi, 2000; Hodges & Kim, 2000). The discriminant validity of CAFAS has also been verified to differentiate between psychiatric inpatient clients and children in alternative care, and it was found to be useful in predicting the utilization of psychiatric services (Hodges, Wong, & Latessa, 1998).

Child Behaviour Checklist (CBCL; Achenbach, 1992) measures child behavioural and emotional problems. These problems include anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behaviour, and aggressive behaviour. The CBCL has good psychometric properties and is regarded as the "Gold Standard" for evaluating child behavioural and socio-emotional problems (Achenbach & Rescorla, 2001). Its reliability and validity, both convergent and discriminant, have been well documented (Dutra, Campbell, & Westen, 2004).

Table 1. Participant characteristics (N = 99)

Characteristics	Mean	SD	(Range)
Age in years at admission	11.97	2.35	(6-17)
Average number of medications per client	1.96	0.91	(1-6)
Average number of medication types per client	1.82	0.78	(1-5)
Average number of diagnoses per client (*n* = 65 clients with a diagnosis)	4.23	2.36	(1-11)

Table 2. Reports of adverse effects (AE) in the study

Type of AE	Total number reported	Percent of weeks with at least one AE
Common	1138	53.3%
Infrequent	439	27.8%
Rare but serious	12	1.8%

Procedure

At the time of referral, the BCFPI was conducted with the child's primary caregiver. Prior to admission, the primary caregiver also completed a battery of standardized psychological health assessments, including the CBCL. The CAFAS was completed by the client's primary clinician at admission and follow-up time points. Prior to discharge, clients were assessed by a psychologist or psychiatrist for mental health disorders using the DSM-IV. The PMMC were completed daily by residential staff (i.e., child and youth workers and nurses) for each client for one to eight weeks during their residential stay. Potential AE were recorded for each day based on staff observations and communication between staff and with clients. Clients were not asked directly if they were experiencing each AE, but any expressed by clients were noted on the checklists. The responsible physician reviewed the PMMC regularly. In the case of weekend or holiday leaves of absence, medication monitoring was temporarily suspended. Therefore, the average number of AE per day for the current analysis was calculated using only the information on the monitored days. Table 1 provides a brief description of client characteristics. Table 2 shows the total number of AE reported during the study, and the percent of weeks with at least one AE reported.

Hierarchical linear modeling (HLM), a complex form of logistic regression was used for the data analyses. HLM was chosen in order to model a nested structure where weeks of monitoring are nested within clients (Woltman, Feldstain, MacKay, & Rocchi, 2012). Weeks of PMMC completion were chosen as a random effect since this number varied among clients for several reasons (e.g., medication prescription changes, admission after the study began, discharge prior to study completion). The dependent variables in the analyses were the average number of AE a client experienced daily within a week and the commonality/severity of such symptoms (common, infrequent, rare but serious). The independent variables were the number of DSM-IV diagnoses and standardized intake scores. Because the variables are highly correlated with each other, the problem of multicollinearity will adversely affect the HLM analyses. Therefore, predictors were placed in the HLM analysis one at a time.

Because each of the standardized intake measures (BCFPI, CAFAS, CBCL) included multiple sub-scores, and because sub-scores across instruments were correlated with each other, factor analyses using a pool of data collected previously from a larger number of clients (N=627) were first conducted to condense these scores into fewer manageable factors. Factor analyses using principal component analyses with direct oblimin were conducted (Yong & Pearce, 2013). Seven factors were extracted because their corresponding eigenvalues were greater than one (Kaiser, 1960). Results are shown in Table 3. The first factor represented problems in impulsiveness, social, thought and attention problems (abbreviated as impulsiveness). The second factor represented conduct problems and substance abuse (abbreviated as conduct). The third factor represented problems in school, work, home, and community setting (abbreviated as setting). The fourth factor represented withdrawn/depressed and somatic complaints (abbreviated as withdrawn). The fifth factor represented issues with cooperativeness, and social functioning (abbreviated as uncooperativeness). The sixth factor corresponded to separation anxiety and anxious/depression problems (abbreviated as anxiety). The final factor represented problems with thinking and self-harm (abbreviated as thinking). All numbers were coded such that a higher score represents more severe problems in the corresponding area. The subscales of the primary participants were transformed into z scores and then amalgamated into the seven factors by taking the mean of the contributing subscales for use in the HLM analyses described below.

Results

Results of the HLM analyses are summarized in Table 4. The first research question was whether the average number of potential AE is predicted by the number of DSM-IV diagnoses. Results showed that the regression coefficient (*B*) relating the number of DSM-IV diagnoses and number of potential AE was positive and statistically significant ($B = 0.17$, $SE = 0.08$, $t = 2.02$, $p = .047$). Next, potential AE were divided into common, infrequent, and rare but serious categories. Similar analyses as above were then conducted. Only for common AE, the regression coefficient continued to show that the number was positively and significantly predicted by the number of DSM-IV diagnoses ($B = 0.09$, $SE = 0.05$, $t = 2.01$, $p = .048$). One may question whether there is a relationship between the number of DSM-IV diagnoses and the number of medication types prescribed (i.e., the number of checklists completed per client within a week). Therefore, another HLM was conducted with the number of DSM-IV diagnoses predicting the number of medication types, but the result was non-significant ($B = -0.11$, $SE = 0.17$, $t = -0.66$, $p = .52$).

An additional area of inquiry was whether the factors derived from the standardized instruments at intake predicted the number of potential AE that clients experienced (i.e., impulsiveness, conduct, setting, withdrawn, uncooperativeness, anxiety, thinking). Again, the problem of multicollinearity among the seven derived factors will affect the HLM analyses and thus only one predicting factor was entered at a time to predict the outcome variable – the number of potential AE. Two out of the seven factors significantly predicted the outcome: impulsiveness ($B = 1.83$, $SE = 0.88$, $t = 2.09$, $p = .048$) and uncooperativeness ($B = 1.38$, $SE = 0.54$, $t = 2.53$, $p = .018$).

Factors that predict the commonality/severity of different AE were then examined. Although there were no significant predicting factors for the number of common AE, uncooperativeness significantly predicted the number of infrequent AE ($B = 0.88$, $SE = 0.27$, $t = 3.27$, $p = .003$). Due to the fact that the reports of rare but serious AE are too few to allow for reliable results, some of the analysis solutions do not converge and thus were not reported in Table 4.

Discussion

The identification of children at highest risk of AE is crucial in guiding future treatment choices and prescribing patterns. There is a need for individualized risk-benefit analysis to minimize AE (Ipser & Stein, 2007). The American Academy of Child and Adolescent Psychiatry (AACAP, 2009) advocates for prescribers to determine the best medication trial for each client, and to educate the client and family about potential AE. We sought to identify individual risk factors that may predict whether a child will experience potential AE during psychopharmacological treatment.

Children diagnosed with a higher number of DSM-IV disorders were more likely to experience a greater number of potential AE, with the number of diagnoses and number of prescribed medication types (i.e., number of PMMC) found to be unrelated. Additionally, two of the seven behavioural factors from standardized intake information (CBCL, CAFAS, BCFPI) significantly predicted the number of

Table 3. Standardized intake instrument analyses

	Factors						
	Impulsiveness	Conduct	Setting	Withdrawn	Uncooperative-ness	Anxiety	Thinking
Brief Child and Family Phone Interview (BCFPI)							
Regulations of attention, impulsivity, and activity	.58						
Cooperativeness					-.78		
Conduct		.53					
Separation from parents						-.74	
Self-harm				.42	-.58		
Global child functioning					-.73		
Global family situation					-.60		
Child and Adolescent Functional Assessment Scale (CAFAS)							
School/work			.50				
Home			.71				
Community			.62				
Behavior towards others			.63				
Moods/emotions			.51				
Self-harmful behavior							.42
Substance use		.79					
Thinking							.85
Child Behaviour Checklist (CBCL)							
Anxious/depressed				.50		-.51	
Withdrawn/depressed				.65			
Somatic complaints				.75			
Social problems	.70						
Thought problems	.69						
Attention problems	.87						
Rule-breaking		.79					

Factor loadings less than .40 were not shown for clarity.

Table 4. Hierarchical linear modeling results for the association between client characteristics and number of adverse effects (AE)

	Total AE			Common AE			Infrequent AE		
Variables	*B (SE)*	*t*	*p*	*B (SE)*	*t*	*p*	*B (SE)*	*t*	*p*
# of DSM-IV Diagnoses	0.17 (0.08)	2.02	.047*	0.09 (0.05)	2.01	.048*	0.07 (0.04)	1.71	.093
Impulsiveness	1.83 (0.88)	2.09	.048*	0.98 (0.49)	2.01	.056	0.84 (0.48)	1.76	.092
Conduct	-0.36 (0.54)	-0.66	.516	-0.17 (0.30)	-0.58	.570	-0.20 (0.29)	-0.68	.503
Setting	-0.44 (0.77)	-0.58	.570	-0.11 (0.43)	-0.26	.796	-0.30 (0.41)	-0.74	.466
Withdrawn	0.59 (0.52)	1.14	.267	0.30 (0.29)	1.04	.308	0.29 (0.28)	1.03	.312
Uncooperativeness	1.38 (0.54)	2.53	.018*	0.48 (0.32)	1.49	.150	0.88 (0.27)	3.27	.003**
Anxiety	-0.15 (0.58)	-0.25	.803	-0.07 (0.32)	-0.21	.835	-0.07 (0.31)	-0.22	.832
Thinking	0.63 (0.48)	1.30	.206	0.46 (0.26)	1.78	.087	0.18 (0.26)	0.69	.495

Note that rare but serious AE analyses are not shown due to low incidence of these types of AE. **p < .01, *p < .05

potential AE experienced: impulsiveness and uncooperativeness. Uncooperativeness further significantly predicted infrequent AE. These factors included signs of decreased willingness to cooperate and reduced social functioning, and may possibly influence adherence to medication treatment thereby affecting AE experiences. Alternatively, impulsiveness and uncooperativeness could lead to multiclass prescribing given the typical challenges involved with managing these clinical symptoms. Others have advised against concomitant administration of multiple medication types (e.g., AACAP, 2009; Safer et al., 2003). Additional caution during client assessment and the formation of pharmacologic treatment plans may thus be warranted. Best practice indicates that psychiatric evaluations must be comprehensive enough to determine psychosocial factors that may prevent a safe medication trial (AACAP, 2009). Our results indicate that there may be ways to predict such complications before they occur. Psychoeducation of impulsive and uncooperative clients and their families may need to emphasize the potential risks of psychotropic medications. As previously mentioned, this may be related to factors such as medication non-adherence or multiclass prescribing given the clinical challenges, which could influence the experience of AE.

Study Limitations

Our study was completed in one tertiary mental health facility serving clients with complex presentations, therefore the generalizability of the findings are limited to facilities that similarly serve children with complex needs. It may be viewed as a limitation that clients were not asked directly about specific AE, and reporting depended on staff observations and spontaneous client report. While training in how to use the PMMC does allow for asking the client how he or she feels, we caution against listing potential AE to clients to avoid false reporting or inducing the potential AE through suggestion. Another limitation of the study was the small number of rare but serious potential AE in our sample. The potential AE were not confirmed as actual AE, which may also limit the generalizability of the findings. Confirmation of AE required the prescribing physician's assessment of the potential AE as a separate task outside of this study's design. It should also be noted that uncooperativeness and impulsive behaviours are often difficult to control using psychotropic medications. Furthermore, these symptoms, commonly found in oppositional defiant disorder and conduct disorder, are often exhibited with comorbid conditions such as ADHD, yielding more complex DSM-IV diagnoses (Humphreys, Aguirre, & Lee, 2012).

Conclusion

The findings of this study indicate that there may be ways to predict whether children are more likely to experience AE from psychotropic medications. If we are able to predict this likelihood during an initial assessment, it can be used to direct and monitor pharmacologic treatment. According to established practice parameters, prescribers are expected to identify which symptoms are best addressed pharmacologically and which are best addressed with psychosocial treatment (AACAP, 2009). Any factors that may impact client safety must be considered. Our findings indicate that uncooperative and impulsive symptoms may be classified as risk factors and may impact prescribing habits if further elucidated.

Clinical Significance

Knowledge of the likelihood of potential AE may impact current clinical practice as it can be of use in the direction and monitoring of treatment, as well as in the education of clients and their families. Greater emphasis should be placed on the risks of pharmacotherapy, and non-pharmacologic options should be fully explored to minimize the risk to these clients. Medication prescribing patterns should be considered with added caution in children who are found to have impulsive or uncooperative behaviours.

Acknowledgements/Conflicts of Interest

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Appendix A

Name:	Casebook#:	Unit:	Week Start Date:
Check all **SSRI** meds given this week:	☐ CELEXA (CITALOPRAM) ☐ CIPRALEX (ESCITALOPRAM) ☐ LUVOX (FLUVOXAMINE)		☐ PAXIL (PAROXETINE) ☐ PROZAC (FLUOXETINE) ☐ ZOLOFT (SERTRALINE)

Instructions: Initial in the correct space for observed side effects. To indicate days when no monitoring took place (i.e., leave of absence) place a line down the length of the column(s).

COMMON:	BASE LINE	MON		TUES		WED		THUR		FRI		SAT		SUN	
		Day	Eve	Day	Eve	Day	Eve	Day	Eve	Day	Eve	Day	Eve	Day	Eve
Appetite Change															
Constipation															
Diarrhea															
Dizziness															
Dry Mouth / Eyes / Nose															
Headache															
Nausea															
Nervousness															
Reflux															
Sleepiness / Tiredness															
Twitching															
Weakness															
INFREQUENT:	BASE LINE	MON		TUES		WED		THUR		FRI		SAT		SUN	
		Day	Eve	Day	Eve	Day	Eve	Day	Eve	Day	Eve	Day	Eve	Day	Eve
Agitation															
Blurred Vision															
Euphoria															
Insomnia															
Irritability															
Rash or Hives															
Restlessness															
Sweating Excessive															
Tremor															
Urination Trouble															
RARE BUT SERIOUS (page physician/ nurse):	BASE LINE	MON		TUES		WED		THUR		FRI		SAT		SUN	
		Day	Eve	Day	Eve	Day	Eve	Day	Eve	Day	Eve	Day	Eve	Day	Eve
Symptoms of Serotonin Syndrome: Confusion, Sweating, Seizure, Agitation, Diarrhea, Tremors, Chest Pain															
Worsened Suicidal Ideation															
Initial for each shift if NO side effects were observed:															
COMMENTS:															

Medical Professional's Initials:_____ Date:_____