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### Assessment of Acute Methylphenidate Toxicity

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#### ABSTRACT

**Introduction**: Despite years of use, there is little data about the toxic dose/effect relationship of methylphenidate. We attempted to identify dose thresholds between different severities of poisoning according to the Poison Severity Score (PSS).

Methods: Retrospective cross-sectional study including all mono-methylphenidate exposures registered by a regional Poison Center between January 2002 and July 2018. We identified 433 cases. Receiver Operating Characteristics (ROC) analyses in different age groups were performed to identify the cut-off with the best sensitivity and specificity in relation to the severity of intoxication by PSS (none/asymptomatic, mild, moderate, severe).

Results: Overall, 392 different individual symptoms were reported. These were the significant cut-off values to differentiate between severity of intoxication: for adults (18 to 65 years) 175 mg for asymptomatic vs. mild intoxications (AUC 0.63, p=0.005). In adolescents (14 to 17 years) 95 mg for asymptomatic vs. mild intoxications (AUC 0.64, p=0.007). In pupils (7 to 13 years) 53 mg for asymptomatic vs. mild intoxications (AUC 0.68, p=0.002). For all age groups it was 95 mg for no/mild symptoms vs. moderate/severe symptoms (AUC of 0.663, p = 0.030).

Conclusion: Our analysis resulted in useful dose cut-off values for methylphenidate exposures to differentiate between asymptomatic and mild intoxications for adults (175 mg), adolescents (95 mg) and pupils (53 mg). Further research in larger cohorts will be needed.

Keywords: Methylphenidate, Acute intoxication, Poison center, Dose thresholds

Abbreviations: ADHD: Attention Deficit/Hyperactivity Disorder; AUC: Area Under the Curve; CI: Confidence Interval; IQR: Interquartile Range; PC: Poison Center; PSS: Poison Severity Score; ROC: Receiver Operating Characteristics; Se: Sensitivity; Sp: Specificity

#### 1. Introduction

In the field of child and adolescent psychiatry, stimulants are one of the most commonly used neuropsychotropic medications<sup>1</sup>. In most Western countries, methylphenidate is currently approved for two indications: Attention-Deficit / Hyperactivity

Disorder (ADHD) and narcolepsy<sup>1,2</sup>. It is an indirect-acting receptor agonist of cellular monoamine transporters, particularly dopamine and norepinephrine transporters, which terminate neurotransmission and therefore are important regulators of noradrenergic and dopaminergic neurotransmission<sup>1,3,4</sup>.

The mechanism of toxicity of methylphenidate is primarily based on excessive extracellular accumulation of dopamine and norepinephrine. Overdose leads to an increased transmitter concentration in the synaptic cleft, causing an overactivation of sympathetic neurons mediated mainly by  $\alpha$ - and  $\beta$ - adrenergic receptors, resulting in a sympathetic nervous system syndrome with pronounced neurological and cardiovascular symptoms<sup>5-9</sup>.

Several research groups have already studied the toxicity of methylphenidate and the clinical effects they describe are largely in agreement. The most reported symptoms include tachycardia, hypertension, palpitations, lethargy, agitation, tremor, mydriasis, psychosis, anxiety/panic and signs of cardiac ischemia<sup>10-12</sup>.

In most studies, no or mild symptoms result from methylphenidate overdose and only occasionally moderate and severe intoxications occur. In severe cases, other substances, like opiates, neuroleptics and tranquillizers, are usually also involved<sup>13</sup>. Nevertheless, there are isolated case reports of severe methylphenidate mono-intoxications resulting in multiorgan failure with rhabdomyolysis, renal failure and pulmonary-, pancreatic- and hepatic insufficiency caused by vasculitis<sup>14-17</sup>.

Despite years of use, the possibility of life-threatening clinical consequences and the demonstration of a statistically significant relationship between dose and outcome, there is little data about the toxic dose / clinical effect relationship of methylphenidate<sup>10</sup>. With this study, we aimed to identify dose thresholds based on the ingested dose corresponding with different severities of intoxication according to the Poison Severity Score (PSS).

#### 2. Material and Methods

This study was designed as a retrospective cross-sectional study and was approved by the local University Ethics Committee (2024-223-S-KK). The dataset used was obtained from the database of a regional Poison Center (PC) in southern Germany. The PC is staffed by experienced medical toxicologists. Our center handles greater than 46,000 calls annually, of which 8,118 in 2023 were consultations from other hospitals. The population served is about 13 million, primarily located in the German state of Bavaria. The dataset comprises all phone calls involving the substance methylphenidate received by the staff of the PC and registered in the database from January 1st, 2002, to July 31st, 2018.

The database was screened for all entries involving the substance methylphenidate during the above-mentioned period. The resulting raw data comprised 1454 entries, after inclusion criteria were applied, 433 records remained. (Figure 1). After descriptive analysis, Receiver Operating Characteristic (ROC) curve analysis was performed to determine the optimal thresholds for predicting the severity of intoxication as a function of ingested dose in each age group (babies (≤ 1 year), infants (2 to 6 years), pupils (7 to 13 years), adolescents (14 to 17 years) and adults (18 to 65 years)).

To provide guidance in determining the most appropriate thresholds, Youden's J index was calculated. Variables with p  $\leq$  0.05 were considered significant.

The dataset was collected in Microsoft Excel and statistical analysis was performed using Microsoft Excel (version 16.77.1, Redmond, WA) and IBM SPSS Statistics for Mac (version 27.0, IBM Corporation, Armonk, NY).

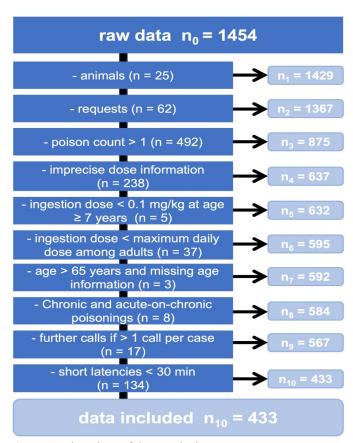


Figure 1: Flowchart of data exclusion process.

#### 3. Results

# 3.1. Characterization of phone call settings, study population and exposures

Of the total of 633,428 documented calls received by the PC during the study period, 1,454 (0.23%) involved methylphenidate and 433 (0.07%) met our inclusion criteria. The number of included calls ranged from 10 calls in 2003 to 42 calls in 2014, with a mean of 25.9 calls per year (SD = 9.2) and a generally increasing trend. Most of the calls were conducted by hospital staff (53.8%), followed by laypersons (20.3%), rescue coordination center staff (12.7%) and general practitioners (8.8%).

Of the total 241 cases with registered sex, most were male (67.2%). The majority of those affected were adults (39.5%), followed by adolescents (24.5%), pupils (22.6%) and infants (12.2%). Only 1.2% of cases involved babies.

In all but one case, the reason for the ingestion of methylphenidate was known. Slightly more than half (50.1%) reported intentional reasons for exposure, including suicidal intent, parasuicidal act and abuse.

By far the most common route of exposure within the analyzed study population was oral ingestion (99.1%). Transmucosal and intravenous administration was reported twice each.

The severity of intoxication according to the PSS score was mild (52.4%) or classified as no or asymptomatic intoxication (44.8%) in most cases. A total of nine adults (5.3%) and two pupils (2.0%) reported moderate symptoms and in the entire study population, there was only one adult (0.2%) suffering from a severe intoxication. (Table 1) provides an overview of the distribution of characteristics by age.

**Table 1:** Distribution of characteristics by age group.

			Age Categories											
		Babies (n = 5)		Infants $(n = 53)$		Pupils (n = 98)		Adolescents (n = 106)		Adults (n = 171)			Total	
		n	%	n	%	n	%	n	%	n	%	n	%	
		Male	1	33.3	16	57.1	44	74.6	40	63.5	61	69.3	162	37.4
Sex		Female	2	66.7	12	42.9	15	25.4	23	36.5	27	30.7	79	18.2
		No / asymptomatic	2	40	30	56.6	65	66.3	44	41.5	53	31	194	44.8
		Mild	3	60	23	43.4	31	31.6	62	58.5	108	63.2	227	52.4
		Moderate	0		0		2	2	0		9	5.3	11	2.5
Severity		Severe	0		0		0		0		1	0.6	1	0.2
		Household accident	5	100	51	96.2	72	73.5	36	34	27	15.8	191	44.1
		Suicidal intent	0		1	1.9	8	8.2	38	35.9	84	49.1	131	30.3
		Parasuicidal act	0		0		7	7.1	16	15.1	25	14.6	48	11.1
		Abuse	0		0		0		11	10.4	27	15.8	38	8.8
Reason Exposure	for	Others	0		1	1.9	11	11.2	5	4.7	7	4.2	24	5.6
		Unknown	0		0		0		0		1	0.6	1	0.2
		Intentional	0		1	1.9	15	15.3	65	61.3	136	79.5	217	50.1
Intention		Unintentional	5	100	51	96.2	79	80.6	37	34.9	31	18.1	203	46.8
		Orally	5	100	53	100	97	99	105	99.1	169	98.9	429	99
Route Exposure	of	Intravenously	0		0		0		1	0.9	1	0.6	2	0.5
		Transmucosal	0		0		1	1	0		1	0.6	2	0.5
		Hospital physicians	2	40	20	37.7	31	31.6	62	58.5	118	69	233	53.8
		Laypersons	1	20	22	41.5	37	37.8	13	12.3	15	8.8	88	20.3
		Rescue coordination center staff	0		2	3.8	10	10.2	16	15.1	27	15.8	55	12.7
		Practitioners	2	40	8	15.1	14	14.3	7	6.6	7	4.1	38	8.8
Caller		Other	0		1	1.9	6	6.1	8	7.5	4	2.3	19	4.4

Overall, the median dose ingested was 80 mg (IQR = 160 mg) for cases classified as no or asymptomatic intoxications, 180 mg (IQR = 320 mg) for mild intoxications and 300 mg (IQR = 380 mg) for moderate intoxications (Figure 2a).

#### 3.2. Clinical consequences of methylphenidate intoxications

Among the analyzed calls, 55.2% described the presence of symptoms (Figure 2a). Neuropsychiatric symptoms (33.8%) and cardiovascular symptoms (26.9%) were reported most frequently, followed by gastrointestinal (9.6%), neurological symptoms (7.4%), symptoms related to the respiratory tract (4.0%) and ophthalmological and dermatological symptoms (2.8%, each).

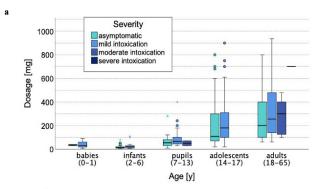
A total of 392 different individual symptoms were reported. The most common among these are displayed in descending order in (Figure 2b).

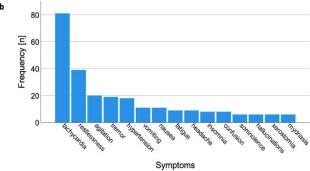
#### 3.3. Determination of dose thresholds (ROC Analyses)

Among babies, exclusively cases of asymptomatic and mild intoxications were reported to the PC. For the ROC curve for these severities (Figure 3a) an Area Under the Curve (AUC) of 0.639 (p = 0.519, 95% confidence interval (95% CI) 0.193 - 1.000) was calculated. The dose of 25 mg (sensitivity (Se) = 0.667 and specificity (Sp) = 0.667) showed the highest Youden's J index.

Within infants, the associated ROC curve (Figure 3b) had an AUC of 0.603 (p = 0.130, 95% CI = 0.482 - 0.724). The Youden's J index was highest (J = 0.187) for the 22.5 mg dose (Se = 0.478;

Sp = 0.709). The dose of 8.75 mg (J = 0.178) showed a better sensitivity (Se = 0.957).





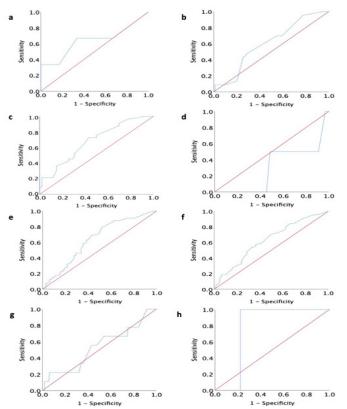
**Figure 2:** Distribution of (a.) Dosage by severity and age group and (b.) Symptoms by frequency.

Cases involving pupils contained not only asymptomatic and mild but also moderate intoxications (Figure 3c and d).

The ROC curve based on asymptomatic and mild intoxications (Figure 3c) had an AUC of 0.680 and was significant (p = 0.002; 95% CI = 0.579 - 0.781). The optimal cut-off value was 53 mg (J = 0.296), with a sensitivity of 0.727 and a specificity of 0.569 and was chosen as optimal threshold. The ROC curve for mild and moderate intoxications (Figure 3d) had an AUC of 0.295 (p = 0.337; 95% CI = 0.000 - 0.642). The dose 67.5 mg had the highest Youden's J index (J = 0.015; Se = 0.5; Sp = 0.515).

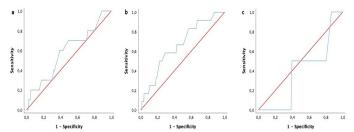
The ROC curve for adolescents (Figure 3e) shows an AUC of 0.638 and was significant (p = 0.007, 95% CI = 0.542 - 0.734). The dose of 95 mg with a sensitivity of 0.800 and specificity of 0.477 had the highest Youden's J index (J = 0.277) and was selected as the optimal threshold to distinguish asymptomatic from mild intoxications in adolescents.

Three ROC curves were generated for the adult age group. The first ROC curve for asymptomatic and mild intoxications is shown in (Figure 3f), had an AUC of 0.628 and was significant (p = 0.005; 95% CI = 0.541 - 0.715). The optimal threshold to discriminate between asymptomatic and mild intoxications in adults was selected at a dose of 175 mg (J = 0.192) with a sensitivity of 0.716 and a specificity of 0.476. The ROC curve based on mild and moderate intoxications (Figure 3g) had an AUC of 0.532 (p = 0.753; 95% CI = 0.327 - 0.737). The Youden's J index was highest at 1150 mg (J = 0.158; Se(c) = 0.222; Sp(c) = 0.936). The ROC curve to distinguish between moderate and severe intoxications (figure 3h) had an AUC of 0.778 (p = 0.384; 95% CI = 0.506 - 1.00). The Youden's J index was highest at 590 mg (J = 0.778; Se(c) = 1; Sp(c) = 0.778).



**Figure 3:** ROC curve of (a.) Babies (asymptomatic / mild intoxication), (b.) Infants (asymptomatic / mild intoxication), (c.) Pupils (asymptomatic / mild intoxication), (d.) Pupils (mild / moderate intoxication), (e.) Adolescents (asymptomatic / mild intoxication), (f.) Adults (asymptomatic / mild intoxication), (g.) Adults (mild / moderate intoxication) and (h.) Adults (moderate / severe intoxication).

The ROC curve for the combined groups asymptomatic and mild versus moderate and severe intoxications among all age groups is shown in (Figure 4a) and has an AUC of 0.663 (p = 0.030) with a 95% CI of 0.516 to 0.810. J was maximal (J = 0.293) at a dose of 290 mg with a sensitivity of 0.583 and a specificity of 0.710. The optimal threshold to discriminate between asymptomatic or mild intoxications and more severe intoxications among all age groups was selected at a dose of 95 mg (J = 0.192) with a sensitivity of 0.833 and a specificity of 0.428. The ROC curve for the combined groups asymptomatic and mild versus moderate and severe intoxications among adults, with an AUC of 0.388 (p = 0.489, 95% CI of 0.071 to 0.705), is displayed in (Figure 4b). The maximal J (J = 0.209) at a dose of 290 mg with a sensitivity of 0.700 and a specificity of 0.509 was selected as an optimal threshold. Finally, (Figure 4c) shows the ROC curve for the combined groups asymptomatic and mild vs. moderate and severe intoxications among pupils. The AUC of 0.388 (p = 0.489) with a 95% CI of 0.071 to 0.705. J was maximal (J = 0.135) at a dose of 27.5 mg with a sensitivity of 1.0 and a specificity of 0.135. The optimal threshold to discriminate between asymptomatic or mild intoxications and moderate or severe intoxications in pupils was selected at a dose of 62.5 mg (J = 0.094) with a sensitivity of 0.500 and a specificity of 0.594.



**Figure 4:** ROC curve of (a.) All age groups with asymptomatic and mild *vs.* moderate and severe (b.) Adults with no and mild *vs.* moderate and severe intoxications (c.) pupils with asymptomatic and mild vs. moderate and severe intoxications.

#### 4. Discussion

Slightly less than half of the methylphenidate exposures we analyzed were either intentional (49.9%) or unintentional (47.1%), which stands in contrast to other studies<sup>18-21</sup>. This may be explained by differences in the study populations and a trend already observed by others regarding the distribution of intentional and unintentional intoxications by age<sup>10,18-21</sup>. While no intentional exposures occurred in infants and young children, they increased steadily with age (schoolchildren: 15.3%, adolescents: 61.3% and adults: 79.5%).

Suicidal intent was the main reason for exposure in the older groups (adolescents: 35.8 %; adults: 49.1%), directly followed by household accidents with 34 % in adolescents and 15.8 % in adults together with cases of abuse. This is confirmed by Jensen et al.<sup>19</sup>, who found that the most common reason for exposure in their adult study population was suicide attempt, while the second most common cause was abuse. The low number of unintentional exposures and abuse among adults can be explained by underreporting due to minor consequences, whereas suicide attempts are probably overrepresented because they are in most cases admitted to hospitals, where medical staff are more likely to refer to a PC for counseling<sup>19</sup>.

Except for four cases reported as intranasal and intravenous administration, almost all exposures we analyzed were oral

ingestions (99.1%), which is in line with previous research<sup>11,19,20</sup>. While the results of Hondebrink et al. <sup>20</sup> shows approximately the same proportions as ours, Jensen et al. <sup>19</sup> and Bruggisser et al. <sup>11</sup> found a higher proportion of alternative routes of administration. One possible explanation for this may be that the majority in their study collective were adults while we focused on children and youths. Since exposure in this group is known to be mostly intentional, including abuse, the intravenous and intranasal administration might be more common<sup>14, 22-26</sup>.

Most of the cases analyzed in our study were asymptomatic or of low severity. This is in line with previous findings<sup>10,11,18,20,21</sup>. In contrast to these studies, describing the range of moderate monointoxications between 8.3 to 18.75%, our study population only comprised 2.5% of moderate cases<sup>10,11,18,21,27</sup>. One reason for this difference may be the small sample size in the above-mentioned studies (16 to 113 cases). Additionally, there were different classification systems used to categorize severity<sup>10,11,18,20</sup>. Still, all studies reported similar low proportions of severe cases with percentages ranging from 0 to 0.3%<sup>10,11,18,21</sup>.

Overall, the median ingested dose increased with age and severity, with the adolescent and adult age group having the highest doses at the various severity levels compared to the younger population groups. This was also observed by Foley et al.<sup>21</sup> Nevertheless, there are some exceptions involving higher severities in the infant and pupil age group, which can be explained by the very low number of cases in these categories.

The median ingested dose of methylphenidate in our study was 108 mg, which is higher than the median dose reported by Hondebrink et al.<sup>20</sup> and White, et al.<sup>10</sup> This may be due to the different age distribution in the individual study populations<sup>28</sup>.

In addition, a wide variation of doses leading to the same severity of intoxication in the same age group can be observed. This may be partly explained by individual differences in sensitivity, pharmacokinetics or genetic differences between different individuals<sup>4,29</sup>. Nonetheless, misreporting by affected individuals or callers may also contribute to the large differences between the minimum dose and the maximum dose registered.

Overall, a broad spectrum of individual symptoms (n=392) was reported in our study. Nevertheless, there is a clear tendency towards either neuropsychiatric or cardiovascular symptoms, which is consistent with other studies<sup>5-9</sup>. Like previous authors, we found tachycardia, hypertension, restlessness, drowsiness, xerostomia and vomiting to be common single symptoms associated with methylphenidate intoxications<sup>10,18,20</sup>. As already described by Klein-Schwartz et al. <sup>18</sup>, symptoms were more likely to occur with increasing age in our collective and correlates with higher doses.

In conclusion, we were able to determine three statistically significant dose thresholds to distinguish between asymptomatic and mild intoxications within pupils (AUC = 0.680, p = 0.002), adolescents (AUC = 0.638, p = 0.005) and adults (AUC = 0.628, p = 0.005) and between asymptomatic and mild versus moderate and severe in all age groups (AUC = 0.663, p = 0.030). Unfortunately, the calculations did not result in statistically significant dose-thresholds for the other age groups and severities.

#### 5. Limitations

Compared to the currently available literature, our study is one of the few that exclusively analyzes mono-intoxications with methylphenidate, which has the advantage that the results found can be attributed solely to methylphenidate toxicity. Apart from this, the relatively high number of included cases due to the long study period increases the significance of the results.

Nevertheless, there are some limitations, some of which are due to the retrospective study design. An information bias results from the fact that the information on cases of intoxication is based on the callers' statements without an objective evaluation.

Given the high number of medical staff calling, reports of more severe methylphenidate intoxications may be overrepresented in our study cohort. Thus, both reporting bias and inclusion bias cannot be ruled out.

In addition, missing information from callers may lead to incomplete data collection and the information on the dose ingested could not be verified, as there was no laboratory confirmation of methylphenidate exposure. However, in most cases the number of pills ingested was counted and therefore it can be assumed that the quantitative data has a rather high level of accuracy.

Overall, the number of cases of moderate and severe intoxications is too low (2.77%) to perform a valid statistical analysis regarding these severity levels. To increase the number of cases of more severe intoxication with an overall low incidence, further research is needed. A multicenter study that covers a larger catchment area and offers the possibility of including more cases could be a suitable method to counteract this problem.

#### 6. Conclusion

In this retrospective cross-sectional study, we assessed acute intoxications with methylphenidate reported to a local PC between January 2002 and July 2018. Most of the registered cases were asymptomatic or of mild severity and only one severe case was observed, according to the PSS score. The drug was administered orally in almost all cases. While intentional reasons for exposure increased, unintentional reasons decreased with age. The most common symptoms were tachycardia, restlessness, agitation, tremor, hypertension, nausea, vomiting, fatigue, headache, insomnia and confusion.

Moreover, we were able to determine statistically significant dose thresholds to distinguish between asymptomatic and mild intoxications in pupils (53 mg), adolescents (95 mg), adults (175 mg) and 95 mg in the general population to differentiate between no/mild symptoms and moderate/severe symptoms. However, it should be noted that thresholds are only one of several factors that influence the decision-making process regarding therapeutic management of intoxications. In addition, further research is needed to confirm our findings and determine significant thresholds for mild, moderate and severe intoxications.

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