Review

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Posted Date: 27 May 2025

doi: 10.20944/preprints202505.2106.v1

Keywords: substance use disorder; comorbidity; mental disorder; prevalence

 doi:10.20944/preprints202505.2106.v1

Review

Comorbidity Data for Mental Disorders and Substance Abuse/Dependence Are of Little Predictive Value for the Clinical Practice: An Umbrella Review of Systematic Reviews

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Abstract: Among the many mental disorders possibly comorbid with the one of primary interest, substance use disorders (SUDs; i.e., substance abuse/misuse and substance dependence) are of preëminent importance as the dropout rates are much higher for SUD than, say, depression. In order to obtain such a general risk assessment, this author performed an umbrella review, i.e., systematic review of systematic reviews on this topic. Secondary SUDs (SECSUDs) were more frequently found in patients suffering from the following mental disorders (in alphabetical order) than in the general population: Anorexia nervosa, anxiety disorders (any), attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder, depression, dysthymia, generalized anxiety disorder (GAD), pathological gambling, posttraumatic stress disorder (PTSD), and schizophrenia. These findings support the assumptions held by many in the therapeutic community, especially if one considers the consumption of a drug of abuse as self-medication to treat symptoms of the mental disorders listed above. One surprising finding for this author was the low prevalence of SECSUDs in bariatric surgery patients, which was only 4%, i.e., comparable or even lower to general population estimates.

Keywords: substance use disorder; comorbidity; mental disorder; prevalence

Introduction

When screening interested prospective patients/clients for their ability to endure the stress of psychotherapy, to effectively work with the psychotherapist and, thus, to ultimately profit from it, it would be very useful to have data at hand for a general risk assessment regarding treatment dropouts. Among the many mental disorders possibly comorbid with the one of primary interest, substance use disorders are of preëminent importance as, in this author's experience, substance abusing/dependent patients are much more prone to break off (discontinue) psychotherapy (i.e., show a much higher dropout rate) compared to, say, depressive patients without these comorbid disorders. Accordingly, in two excellent Cochrane reviews, the dropout rate for patients treated with cognitive behavioral therapy (CBT) in clinical trials was 36% (178 of 490) for stimulant use disorder [1] vs 11% (18/160) for depression [2]. Although such risk assessment is of interest for all mental health care providers in all treatment settings, it is of special concern for those working in private practice for whom premature termination of treatment by the patients also presents a considerable economic strain to the health care provider.

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When preparing for this review, this author found guidance in the excellent reviews of Schuckit [3] and Clark et al. [4]. Schuckit provided a useful differentiation in that the comorbidity of a substance use disorder and other mental disorders ("*psychiatric syndromes*") is based on four different

 doi:10.20944/preprints202505.2106.v1

trajectories: (1) The disorders are independent of each other. (2) The first disorder influences the development of the second condition. (3) The second condition is a result of the patient's effort "*to diminish problems associated with the first syndrome*". Schuckit focussed on (4) substance-induced syndromes, which is, in my opinion, a variant of trajectory 2.

1.1. Previous Reviews Suggest a Disconcertingly Wide Range of Comorbidity Prevalence/Incidence Data

Schuckit emphasized that "estimates of the prevalence of substance-induced psychiatric syndromes range from about zero … to 65% or more of some psychiatric conditions seen in alcoholics …" [3]. He estimated that "The life-time rate of temporary substance-induced psychoses in stimulant-dependent individuals may be at least 40%." but, unfortunately, did not give a number for the estimate of cannabinoid-induced psychoses. Schuckit also summarized evidence to conclude that "40% or more of alcoholics have histories of major depressive episodes, as many as 70% of these are substance-induced disorders …" [3]. Schuckit estimated the percentage of substance-induced mental disorder as 20% for panic disorders, 25% for social phobias, 40% for obsessive-compulsive disorders and 50% for agoraphobia.

On the positive side, Schuckit noted that "85% or more of substance-induced syndromes improve rapidly with abstinence, falling below the threshold for a diagnosis of an Axis I disorder within several days to a month." [3]. As an orientation for the younger readers of this review: The DSM-IV (diagnostic and statistical manual of mental disorders, fourth edition, DSM4)[5] categorized the clinical disorder "or other conditions that may a focus of clinical attention" in axis I (one), whereas personality disorders (or mental retardation) were grouped in axis II (two), a practice that has been abandoned in the DSM-5 (DSM5) [6].

Schuckit [3] also emphasized that this rapid remission is clearly different from other primary mental disorders: "*This clinical course is distinct from what would be expected with, for example, independent schizophrenia and major depressive episodes.*" This insight should encourage us to differentiate primary from secondary, i.e., substance-induced, symptoms of our patients, not least to give more hope to them in the case of substance-induced suffering.

1.2. Primary vs Secondary Substance Use Disorder Comorbidity (PRIMSUD vs SECSUD)

Another landmark publication for this author was a study of 207 treatment-seeking cocaine abusers by Halikas and coworkers [7]. Although these authors excluded individuals with a previous diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorders or those currently taking any antipsychotic (neuroleptic), or antidepressants of the tricyclic (TCA) or monoamide oxidase inhibitor (MAOI) group, benzodiazepine "or any other psychotropic medication (page 26 of [7]), their findings were remarkable: 62% (current) and 73% (lifetime) of these patients met the diagnostic criteria for any psychiatric disorder, the prevalence rank order of specific disorders being (current – lifetime prevalence):

antisocial personality disorder (ASPD; no data – 40%)
alcohol (37 – 75%)
any other drug diagnosis (excluding nicotine, alcohol, marijunana and cocaine; 33 – 67%).
any anxiety disorder (including panic, GAD, phobia and OCD) (30 – 37%)
marijuana (29 – 55%)
phobia (27 – 34%)
nicotine dependence (21 – 66%)
posttraumatic stress disorder (PTSD; 18 – 27%)
any affective disorder (including depression, dysthymia and mania)
major depression (16 – 23%)
gambling (9 – 12%)
dysthymia (4 – 11%)
obsessive-compulsive disorder (OCD; 4 – 5%)
panic disorder (3-6%)

 doi:10.20944/preprints202505.2106.v1

generalized anxiety disorder (GAD; 2-3%)
manic episode (1 – 2%)

Obviously, these 207 surveyed treatment-seeking cocaine abusers showed very high rates of problems with other drugs of abuse, most notably alcohol (ethanol). Surprisingly for this author, gambling (as a non-drug stimulus with abuse liability) ranked very low in this sample. Among other psychiatric diagnosis, the highest prevalence rates wer found for antisocial personality disorder (ASPD), phobia, posttraumatic stress disorder (PTSD) and major depression. Interestingly, the prevalence of ASPD war significantly higher in men than women (45 vs 29%). For all other psychiatric comorbidities, women ranked higher than men (table 4 [7].

Halikas and coworkers (1994) also differentiated (their Table 7) three temporal orders, with the psychiatric diagnosis preceding, occurring at the same time, or following the first regular use of cocaine or other drugs of abuse, cocaine or other drug problems, and an abuse diagnosis for cocaine or other drugs of abuse. Whenever the psychiatric diagnosis preceded the drug use/abuse diagnosis, these authors declared it the "*primary*" disorder and discussed that the subsequent, i.e., secondary substance use disorder (abbreviated SECSUD in the following)"would be seen as an attempt to "self-medicate" (quotation marks by [7]) the psychiatric symptoms". If the substance use disorder preceded the psychiatric diagnosis, it war considered "primary" (PRIMSUD in the following). Halikas et al offered the following explanation: "… substance abuse may trigger the development of psychopathological conditions in some individuals." (p.31 of [7]). First regular cocaine use was **preceded** in 57% by any affective disorder and in 88% by any anxiety disorder (SECSUD), whereas the respective psychiatric diagnosis **followed** the first regular cocaine use (PRIMSUD) in only 40% (affective) and 9% (anxiety), respectively. The respective rates for the first regular use of other drugs are 26% (affective) and 77% (anxiety) for SECSUD and 65% (affective) and 20% (anxiety) for PRIMSUD. Halikas et al [7] summarized and emphasized their findings as follows (their p.32): "*Of particular interest is the finding that anxiety disorders precede the first regular use of any drug of abuse in over 76% of the subjects; in contrast, almost 65% of the subjects report their first regular drug use prior to the onset of affective disorders.*" This authors suggests the following simplified conclusion: More individuals took drugs of abuse to treat their primary affective disorder, mainly depression, and their anxiety, i.e., used the drug of abuse to self-medicate (SECSUD). Cocaine was only the slightly preferred anxiolytic drug of abuse even among treatment-seeking cocaine abusers. Fewer individuals used drugs of abuse for other reasons than self-medication of another primary mental disorder. Both groups paid the price of drug-induced depressive symptoms and, to a lesser degree, anxiety, most likely during the withdrawal phase. To summarize, the distinction between PRIMSUD and SECSUD was based on the temporal order of the first description of the respective symptoms / diagnosis, whereas reliably establishing a causal relationship has, in this authors opinion, still not been achieved in the respective studies.

This review also set out to determine if the results published by Halikas et al in 1994 in their original study [7] and their conclusions would be confirmed by the plethora of systematic reviews generated within the next 31 years.

Methods

This umbrella review (i.e., systematic review of systematic reviews) followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; https://www.prisma-statement.org/ [8]). Interestingly, combining the search terms ("substance abuse" or "substance use" or "substance misuse") with only ("mental disorder" or "psychiatric disorder") was unsatisfactory, i.e., did not capture "depression". Therefore, this author consulted the International classification of Diseases, 11th revision (ICD11; https://icd.who.int/en/) and extracted all diagnoses given in section 06 ("Mental, behavioural or neurodevelopment disorders" of the ICD11. Remarkably, this search yielded a database that did not include any articles referring to the "epidemiological catchment area (ECA)" or "national comorbidity survey (NCS)", i.e., surveys that, in this author's opinion, have greatly contributed to our understanding of the comorbidity of

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substance abuse and dependence with other mental disorders. On the other hand, the number of hits for reviews in general (145,937) proved to be overwhelming both for the software used ("*Only the first 10,000 citations will be saved in our file*" https://pubmed.ncbi.nlm.nih.gov/, accessed 20250109) and this author. Therefore, the search was restricted to systematic reviews. The final number of pubmed hits (11 duplicates removed) was 3,611. The author added 4 publications from his own database. The interested reader can obtain a detailed description of the search terms used and the searchers from the author (office@zerniglabor.at). Applying the principle of maximal scientific transparency, the author first focused on those articles that gave concrete numbers already within the abstract proper.

Results

Table 1. shows the prevalence or odds ratios for substance use disorders that were independent of the other mental disorders or a consequence of it, i.e., can be considered secondary substance use disorder (SECSUD), whereas Table 2 shows mental disorders that were proposed by the authors of the respective systematic review to be the cause for another mental disorder, i.e., can be considered primary substance use disorders (PRIMSUD).

Table 1. PRIMARY mental disorder, SECONDARY substance use disorder (SECSUD). Primary mental disords are listed in alphabetical order. Abbreviations: %, prevalence as percent of study population; CI, 95% confidence interval; na, data not available; Ni, total number of individuals in Ns numbers of studies; OR, Odds Ratio.

Mental disorder [ICD10/11 codes]	Comorbidity [given as % prevalence or as Odds Ratio with 95% confidence interval]	Ni individuals in Ns studies	Comments [reference]
Anorexia nervosa, restrictive (ANR) vs binge-eating/purge (ANBP) type	substance use disorder 16% AN overall 18% ANBP 7% ANR drug abuse/dependence disorder 9% ANBP 3% ANR alcohol abuse/dependence 15% ANBP 3% ANR cannabis use/dependence 4% ANBP 0% ANR AN overall: 37% caffeine use 29% alcohol use 25% tobacco 14% cannabis	14,695 in 52	[9]
Anxiety disorder (any)	illicit drug use OR 2.91 (2.58-3.28 CI) alcohol use disorder OR 2.11 (2.03-2.19 CI)	na	[10]
Attention-deficit hyperactivity disorder (ADHD)	cannabis use disorder (prediction interval) 19.2% (12.4-48.8) current 26.9% (5.5 – 39.1) lifetime	na in 14	14 articles analyzed [11]

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Attention-deficit hyperactivity disorder (ADHD)	cocaine use 26.0% (18-35 CI) cocaine use disorder 10.0% (8.0-13.0 CI)	na in 12	[12]
Autism spectrum disorder (ASD; ICD10, DSM)	alcohol use disorder 1.6% population register 16.1% clinical setting	389,281 in 22 pooled: 83% male, 32yr (median of mean)	Ni pooled: 83% male, 32yr (median of mean)[13]
Bariatric surgery patients	substance use disorder 4.3%	na in 7	3242 studies analyzed, only 7 met inclusion criteria [14]
Bipolar disorder	alcohol use disorder 29.1% alcohol abuse 18.7% alcohol dependence 15.9%	32,886 in 20 of which 13,963 male (42%), 17,923 female and 1,000 neither male nor female	13,963 male (42%), 17,923 female and 1,000 neither male nor female [15]
Bipolar disorder	24% (18-29 CI)	51,756 in 53	[16]
Bipolar disorder	male OR 2.191 (1.121-4.281 CI) number of manic episodes no OR in abstract previous history of suicidality OR 1.758 (1.156-2.674 CI) not related to age, subtype of BD, hospitalization or coexistence of anxiety disorder or psychotic symptoms	na	na [17]
Bipolar disorder	alcohol use 42% cannabis use 20% illicit drug use 17%	na in 22 multisite and 56 monosite studies	[18]
Depression	cannabis dependence OR 4.9	na in 120	[19]
Depression	depressed individuals: 16% current alcohol problems (range 5-67%) 30% lifetime alcohol problems (range 10-60%) general population: 7% current alcohol problems 16-24% lifetime alcohol problems	na in 35	median current vs lifetime prevalence no statistics given [20]

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Depression (major depressive disorder)	any substance use disorder 25% (36% in men vs 19% in women, OR 2.628, 2.502-2.76 CI) alcohol use disorder 20.8% illicit drug use disorder 11.8% cannabis use disorder 11.7%	348,550 in 48	[21]
Depression (major)	cannabis use disorder (CUD) OR 3.22 (2.31-4.49 CI)	na in 67	not stated if 12mo or lifetime prevalence [22]
Depression (major)	illicit drug use OR 3.80 (3.02-4.78) alcohol use disorder OR 2.42 (2.22-2.64 CI)	na in 22	[10]
Dysthymic disorder	drug dependence OR 11.3	na in 120	[19]
General population (USA)	mood disorders 9.21% (8.78-9.84 CI) anxiety disorders 11.08% (10.43-11.73 CI) substance use disorders 9.35% (8.86-9.84 CI)	na	12-month prevalence *"Only a few individuals with mood or anxiety disorder were classified as having only substance-induced disorders"* [23]
Generalized anxiety disorder (GAD)	2.99 (2.14 – 4.16 CI) cannabis use disorder	na in 67	not stated if 12mo or lifetime prevalence [22]
Mood disorder (broadly defined)	drug dependence OR 5.7	na in 120	[19]
Pathological gamblers	nicotine dependence 60.1% substance use disorder 57.5%	na in 11	[24]
Personality disorders: antisocial (AS), borderline(BL), other (Ot), undifferentiated (Ud)	lifetime alcohol use disorder 76.7% AS 52.2% BL 38.9% Ot or Ud no difference between clinical vs population sample	na in 16	[25]
Posttraumatic stress disorder (PTSD)	1.9-11.3% substance use disorder	na in 24	Veterans 60+ yr [26]

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Posttraumatic stress disorder (PTSD)	24.0% current tobacco use in PTSD vs 20.2% PTSD among tobacco users	na in 66	primary vs secondary substance use [27]
Posttraumatic stress disorder (PTSD)	9.8-61.3% alcohol misuse in PTSD 2.0-63.0% PTSD in alcohol misusers	na in 42	primary vs secondary substance use [28]
Schizophrenia	any substance use disorder 41.7%, 48% in male vs 22.1% in female, OR 3.43, 3.01-3.92 CI) illicit drug use disorder 27.5% cannabis use disorder 26.2% alcohol use disorder 24.3% stimulant use 7.3%	165,811 in 123	[29]
Schizophrenia	pathological gambling range, 0.32 – 19.3% majority of studies, 6.4 – 17& 5-25times higher than in the general population	1,116,103 in 16	mostly male, mean 40yr [30]
Schizophrenia: Individuals at clinical high risk for psychosis	Amphetamine use disoders 1% (0-3% CI) Any substance use disorder 11% (9-13% CI) Alcohol use disorder 8% (5-10% CI) Cannabis use disorder 3% (10-16% CI) Stimulants use disorder 3% (1-6% CI) Any eating disorder 3% (2-3% CI) Cocaine use disorder 1% (0-3% CI) Opioid use disorder 1% (0-3% CI)	na in 312 1457 in 3 4897 in 45 2780 in 23 3119 in 25 199 in 2 3843 in 30 1486 in 4 223 in 3	312 studies total Table 1 [31]
Schizophrenia: Individuals at clinical high risk for psychosis	48.7% lifetime cannabis use 25.8% current cannabis use risk of transition to psychosis not significantly different ie 1.11 RR, 0.89-1.37 CI)	na	20.1yr 58.4% male [32]

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Table 2. Substance use disorder considered primary, PRIMSUD-induced mental disorder considered secondary. PRIMSUDs are listed for each pharmacologic agent in alphabetical order. In the case of ethanol, the much more commonly use descriptor "alcohol" is used. For abbreviations see legend to Table 1.

Primary substance use disorder [ICD10/11 codes]	Comorbidity	Ni individuals in Ns studies	Comments [reference]
Alcohol dependence	Alcohol-induced psychotic disorder (AIPD) 0.4% general population 4.0% patients with alcohol dependence	na in 21	lifetime prevalence [33]
Alcohol dependence	ca 11% social anxiety disorder	na	[34]
Kath users	122% increased prevalence (OR 2.22, 1.76-2.79 CI)	na in 35	[35]
Opioid use disorder (OUD)	current depression 36.1% (32.4 – 39.7 CI) anxiety 29.1% (24.0-33.3) ADHD 20.9 (15.7-26.2) PTSD 18.1 (15.4-20.9) Bipolar disorder 8.7 (6.7-10.7) lifetime antisocial PD 33.6 (29.1-38.0) borderline PD 18.2 (13.4-23.1)	104,135 in 345	[36]
Psychotic symptoms in synthetic cathinone (bath salt) users	38% (29 – 48 CI)	na in 32	[37]
Substance abuse	Depersonalization-derealization disorder (DDD) in: substance abuse 1.8 – 5.9% 0 – 1.9% general population 5-20% outpatients 17.5 – 41.9% inpatients	na in 23	[38]
Substance use, treatment seekers	any current mental disorder 47-100% Depression 27-85% Generalized anxiety disorder 1-75%	na in 18	Australian samples [39]

Discussion

As it is of greater importance for the consulted psychotherapist, clinical psychologist. psychiatrist or other health care provider to know that a patient with a mental disorder is also burdened with a substance use disorder that can be considered a symptom of this mental disorder, i.e., is a secondary substance use disorder (SECSUD), the SECSUDs will be discussed first. A scenario

 doi:10.20944/preprints202505.2106.v1

in which the substance use disorder is independent of the mental disorder that led the patient to seek help seems to be more unlikely and will thus be discussed further down.

SECSUDs were more frequently found in patients suffering from the following mental disorders (in alphabetical order) than in the general population: Anorexia nervosa, anxiety disorders (any), attention-deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), bipolar disorder, depression, dysthymia, generalized anxiety disorder (GAD), pathological gambling, posttraumatic stress disorder (PTSD), and schizophrenia. These findings support the assumptions held by many in the therapeutic community, especially if one considers the consumption of a drug of abuse as self-medication to treat symptoms of the mental disorders listed above.

One surprising finding for this author was the low prevalence of SECSUDs which was only 4% in bariatric surgery patients, i.e., comparable or even lower to general population estimates, in bariatric surgery patients, because this author had assumed that the general vulnerability for abuse/dependence, well-known to apply across various pharmacologic groups of drugs of abuse (polysubstance use), would also be applicable to food and drugs.

Among personality disorders (PDs), antisocial as well as borderline, other PDs or undifferentiated PDs showed a higher prevalence of (comorbidity with) substance use disorders. For many therapists, this is not surprising from the conceptual viewpoint, as substance abuse/misuse is considered a symptom and thus, a part of, at least the borderline personality disorder according to DSM5 and ICD10. The precise diagnostic situation is as follows):

Antisocial/dissocial PD: SUDs are not listed as a symptom in antisocial PD according to DSM5 301.7 or dissocial PD according to ICD10 F60.2. When searching for "antisocial personality disorder", ICD11 lists a "6D10.Z Personality disorder, severity unspecified" and gives "antisocial personality disorder as a "matching term", but does not yield any specific symptoms https://icd.who.int/browse/2025-01/mms/en#941859884%2Funspecified accessed 20250430).

Borderline PD: Substance abuse is explicitly listed as symptom number 4 according to DSM5 301.83. The ICD10 definition of emotionally unstable personality disorder F60.3 lists "*lack of impulse control*" in F60.30 "*impulsive type*" and "self-harm" in F60.31 ("*borderline type*"). ICD11 describes "6D11 prominent personality traits or patterns" and gives a "6D11.5 Borderline pattern" that includes "marked impulsivity", "recurrent episodes of self-harm", without, hower, listing substance abuse explicitly.

Other PD or Undifferentiated PD: DSM5 lists "301.89 Other specified Personality Disorder" and declares it to be equivalent to ICD10 F60.89 and identifies and "301.9 Unspecified Personality Disorder" equivalent to ICD10 F60.9. ICD10 lists a "F60.9 personality disorder, unspecified" and a "F62.9 Enduring personality change, unspecified". ICD10 lists a "F60.9 personality disorder, unspecified" and a "F62.9 Enduring personality change, unspecified". of the abovementioned diagnoses gives a specific symptom description, let alone the mentioning of substance use.

In the case of primary substance use disorders (PRIMSUD) leading to other – secondary – mental disorders, the findings of the analyzed studies do not provide any surprises: All secondary mental disorders can easily be explained as withdrawal symptoms of the respective pharmacologic group of the abused drug.

As mentioned above, this review also set out to determine if the results published by Halikas et al in 1994 in their original study [7] and their conclusions would be confirmed by the plethora of systematic reviews generated within the next 31 years. Unfortunately, many systematic reviews only gave Odd Ratios (ORs) and no % prevalence data, rendering a direct comparison impossible (e.g., in the case of anxiety disorders and SECSUD; Table 1). In a systematic review of Australian samples of treatment seeking substance users [39], the prevalence rates of any current mental disorder, depression, and generalized anxiety disorder (GAD) were comparable to the high prevalence rates given in the original study by Halikas and coworkers 31 years ago [7] and by Schuckit and coworkers 19 years ago [3]. Similarly high prevalence rates were also found for SECSUDs in opioid use disorder (Table 2).

 doi:10.20944/preprints202505.2106.v1

Conclusions

With the notable exception of bariatric surgery patients, secondary substance use disorders (SECSUD) were found in a large number of mental disorders for which the consumption of a drug of abuse can be considered self-medication. Among personality disorders, the increased prevalence of SECSUD in borderline personality disordered patients can be easily explained by the fact that substance abuse/misuse is among the diagnostic symptoms of this disorder. In the case of primary substance use disorders (PRIMSUD) leading to other – secondary – mental disorders, the documented disorders can easily be explained as withdrawal symptoms of the respective pharmacologic group of the abused drug.

With respect to helping the therapist to evaluate patients with respect to their ability to endure the stress of psychotherapy because of a SECSUD, the systematic reviews reviewed in the present umbrella review do not provide any meaningful quantitative basis. Therefore, they are unfortunately of little predictive value for the clinical practice.

Conflicts of Interest: The author declares no conflict of interest.

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 doi:10.20944/preprints202505.2106.v1