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The Diagnostic clinical Interview for Drug Withdrawal 1 (DID-W1) – New Symptoms of Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Reuptake Inhibitors (SNRI): inter-rater reliability

La Diagnostic clinical Interview for Drug Withdrawal 1 (DID-W1) – New Symptoms of Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Reuptake Inhibitors (SNRI): affidabilità fra valutatori

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SUMMARY. Aim. A wide range of clinical phenomena have been reported with dose reduction or drug discontinuation of Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Reuptake Inhibitors (SNRIs). In 2015, a new classification of SSRIs/SNRIs withdrawal (i.e., new withdrawal symptoms, rebound symptoms withdrawal, persistent post-withdrawal disorders) was outlined on the basis of the literature and clinical observations. A semistructured clinical interview, the Diagnostic clinical Interview for Drug Withdrawal 1 - New Symptoms of SSRI and SNRI (DID-W1), was developed for identifying and differentiating such syndromes. Its inter-rater reliability has been tested. **Methods.** Seventeen consecutive outpatients with a history of SSRI or SNRI dose reduction or discontinuation were assessed independently by 2 clinicians at different times during the same day. Percent agreement, Cohen's kappa, and the squared correlation coefficient were used to measure inter-rater reliability. **Results.** The percent agreement for the whole interview was 97.06%, the Cohen's kappa 0.85 (95% CI of 0.61-1.08), the squared correlation coefficient 0.72. **Discussion and conclusions.** The kappa values indicated excellent inter-rater agreement. Validity evaluation and comparison with other instruments need to be performed. The DID-W1 may help diagnosing the clinical phenomena related to SSRI and SNRI discontinuation, their differentiation from relapse, and the potential iatrogenic origin of psychiatric symptoms in clinical practice.

KEY WORDS: withdrawal, selective serotonin reuptake inhibitor, serotonin norepinephrine reuptake inhibitor, interview, reliability, iatrogenic comorbidity.

RIASSUNTO. Scopo. Dopo la riduzione della dose o la sospensione di Selective Serotonin Reuptake Inhibitors (SSRI) o di Serotonin Norepinephrine Reuptake Inhibitors (SNRI) si possono verificare molti fenomeni clinici. Nel 2015, è stata delineata una nuova classificazione delle sindromi d'astinenza da SSRI/SNRI (cioè, nuovi sintomi, rimbalzo, disturbi persistenti post-astinenza) sulla base della letteratura e delle osservazioni cliniche. Un'intervista clinica semistrutturata, la Diagnostic clinical Interview for Drug Withdrawal 1 - New Symptoms of SSRI and SNRI (DID-W1), è stata sviluppata allo scopo di identificare e differenziare queste sindromi. La sua affidabilità fra valutatori è stata testata. **Metodi.** Diciassette pazienti ambulatoriali consecutivi con una storia di riduzione o sospensione di SSRI o SNRI sono stati valutati indipendentemente da 2 clinici in tempi diversi dello stesso giorno. La percentuale di accordo, il kappa di Cohen e il quadrato del coefficiente di correlazione sono stati utilizzati per misurare l'affidabilità fra i valutatori. **Risultati.** La percentuale di accordo fra i valutatori relativamente all'intera intervista è risultata pari al 97,06%, il kappa di Cohen è risultato pari allo 0,85 (IC95% di 0,61-1,08), il quadrato del coefficiente di correlazione è risultato pari allo 0,72. **Discussione e conclusioni.** I valori di kappa indicano un eccellente accordo fra i valutatori. Sono opportune ulteriori indagini sulla validità e confronti con altri strumenti. La DID-W1 può aiutare a diagnosticare i fenomeni clinici collegati alla sospensione di SSRI e SNRI, a differenziarli dalla ricaduta e a identificare l'origine potenzialmente iatrogena dei sintomi psichiatrici nella pratica clinica.

PAROLE CHIAVE: astinenza, inibitori selettivi della ricaptazione della serotonina, inibitori della ricaptazione di serotonina e noradrenalina, intervista, affidabilità, comorbilità iatrogena.

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INTRODUCTION

In 1968, Di Mascio and Shader introduced the concept of behavioral toxicity of psychotropic medications which referred to the pharmacologic actions of a drug that, within the range in which it has been found to possess clinical utility, may produce alterations in mood, perceptual, cognitive, and psychomotor functions that limit the capacity of the individual or constitute a hazard to well-being[1-3]. In 1980, Perl and co-authors reviewed this concept discussing the mechanisms by which psychotropic drugs can cause adverse reactions, that is through the extension of their primary therapeutic action and/or the onset of secondary actions as well as withdrawal, dependence, and tolerance symptoms[4]. The concept of drug-induced illness was reported by Chouinard et al.[5,6] during antipsychotic withdrawal or switch, using the model of neuroleptic-induced tardive dyskinesia with the sub-types of withdrawal, overt, masked, and persistent[7]. The same concepts were applied to antidepressant withdrawal[8,9] and Fava et al.[10] defined a form of behavioral toxicity as iatrogenic comorbidity providing differentiation between adverse or emergent events that are limited to the period of psychotropic drug administration and effects that may persist long after drug discontinuation[10]. They suggested that psychotropic drug treatment, particularly after long-term use, may increase the risk of experiencing additional psychological problems or of modifying responsiveness to subsequent treatments[11].

There is a consistent body of knowledge that indicates that dose reduction or discontinuation of Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Reuptake Inhibitors (SNRI) induces a number of clinical phenomena (i.e., withdrawal or discontinuation syndromes, rebound symptoms, persistent post-withdrawal disorders) both in adults and in children[12-20]. There have been various definitions[17,21,22] as well as diagnostic criteria[23,24] of these clinical phenomena. In 2015, a comprehensive and new classification of SSRIs/SNRIs withdrawal phenomena was outlined and specific diagnostic criteria were proposed[9], they allow to formulate the diagnosis of three different syndromes: new symptoms, rebound, persistent post-withdrawal disorders[9] (Table 1). The prevalence of these syndromes is not known at the moment, due to their very recent definition and a lack of diagnostic tools.

Table 1. Withdrawal syndromes according to Chouinard & Chouinard's criteria[9]: new symptoms, rebound, persistent post-withdrawal disorders.

New symptoms	Symptoms not present before the beginning of the SSRI/SNRI treatment and before reduction or discontinuation of the drug	• short-lasting • reversible *Unspecific symptoms*: nausea, headaches, tremor, sleep disturbances, decreased concentration, anxiety, irritability, agitation/aggression, depression/dysphoria *Specific serotonin-related symptoms*: flu-like (e.g., flu), cardiovascular (e.g., tachycardia), gastrointestinal (e.g., diarrhea), neuromuscular (e.g., myoclonus), sensory (e.g., electric shock sensations), cognitive (e.g., confusion), sexual (e.g., premature ejaculation)
Rebound	The return of symptoms which were present before the beginning of the SSRI/SNRI treatment but not present before reduction or discontinuation of the drug	• more intense than before treatment • rapid • transient • reversible • may be associated to the psychological belief of the need of the drug • improve rapidly after reintroduction of the drug
Persistent post-withdrawal disorders	The return of symptoms which were present before the beginning of the SSRI/SNRI treatment but were not present before reduction or discontinuation of the drug or of the return of the original illness with additional symptoms (e.g., melancholic features for depression) or appearance of symptoms related to emerging new mental disorders	• persist longer than 6 weeks after dose reduction or drug discontinuation • have greater intensity than before treatment • partially or totally reversible • respond partially or totally to reintroduction of discontinued drug

METHODS

Instrument

The Diagnostic clinical Interview for Drug Withdrawal 1 - New Symptoms of SSRI and SNRI, identified with the acronym DID-W1, is a brief semi-structured clinical interview which allows the diagnosis of withdrawal of SSRI or SNRI according to Chouinard & Chouinard[9]. It is conducted as a clinical interview by a properly trained clinician and is divided in five modules:

- the first module (named DID-W1-PD) includes 13 questions collecting socio-demographic (e.g., date of birth, sex, civil status, education) or clinical information (i.e., current psychiatric disorder, current psychotropic medication use);
- the second module (named DID-W1-SQ) includes screening questions on the lifetime use of SSRI/SNRI (2 general questions and 4 questions for each SSRI/SNRI used);
- the third module (named DID-W1-WS1) allows to formulate the diagnosis of current as well as lifetime new symptoms (26 questions in section a, 27 questions in section b);
- the fourth module (named DID-W1-WS2) allows to formulate the diagnosis of current as well as lifetime rebound (14 questions in section a, 15 questions in section b);
- the fifth module (named DID-W1-WS3) allows to formulate the diagnosis of current as well as lifetime persistent post-withdrawal disorders (12 questions in section a, 13 questions in section b).

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Modules DID-W1-WS1, DID-W1-WS2, DID-W1-WS3 include two sections each (section a, section b) which allow to formulate the current (section a) and the lifetime (section b) diagnosis of each disorder. Table 2 reports the first question of module DID-W1-WS1 section as an example.

Each section of modules DID-W1-WS1, DID-W1-WS2, DID-W1-WS3 is structured as follows:

- the first column (named "CURRENT/LIFETIME name of the syndrome") suggests the clinical interviewer the question to formulate;
- the second column (named "DIAGNOSTIC CRITERIA) (CHOUINARD AND CHOUINARD, 2015)") reports the specific diagnostic criterion according to Chouinard & Chouinard[9] which can be investigated with the question proposed in the first column;
- the third column (named "ANSWER") is the space where the clinical interviewer reports the answer;
- the fourth column (named "INSTRUCTION FOR THE INTERVIEWER") describes the instruction which must be followed by the clinical interviewer to conduct the interview.

The rater answers YES/NO. The diagnostic algorithm produces the final diagnoses. At the end of each section a and b, a diagnostic box is provided where the clinical interviewer ticks whether the diagnostic criteria were satisfied or not.

The items of the DID-W1 were derived from well-known and validated diagnostic interviews and scales: the Structured Clinical Interview for DSM-5, Clinician Version, SCID-5 -CV[26]; the Mini International Neuropsychiatric Interview (MINI) 7.0.2[27]; the Clinical Interview for Depression[28]; the Richmond Agitation-Sedation Scale[29]; the Beck Depression Inventory-II[30,31]; the Extrapyramidal Symptom Rating Scale[31]; the Positive and Negative Syndrome Scale[32]; the Somatic Symptom Scale-8 (SSS-8)[33]; the State Trait Anxiety Inventory – Form Y[34]; the Psychosocial Index[35,36].

Data collection

Seventeen consecutive self-referred outpatients with a history of SSRI or SNRI reduction or discontinuation were assessed by 2 clinicians (1 psychiatrist, 1 clinical psychologist) independently at different times during the same day. This was an adequate sample size for the purpose of validating the interview[37]. All patients were studied at the Department of Health Sciences of the University of Florence. The mean age was 43.18 years (SD=11.21 years, range 26-63 years), they were 8 males and 9 females. The patients had received the antidepressants to treat (diagnoses formulated via the SCID-5 -CV)[26]: major depressive episode (n=5; 29.41%), major depressive disorder (n=3; 17.65%), panic disorder (n=3; 17.64%), panic disorder and agoraphobia (n=3; 17.64%), panic disorder and major depressive episode (n=1; 5.88%), obsessive-compulsive disorder (n=1; 5.88%), schizoaffective disorder (n=1; 5.88%). The patients had been treated with paroxetine (n=6; 35.29%), sertraline (n=5; 29.41%), citalopram (n=2; 11.76%), escitalopram (n=2; 11.76%), fluvoxamine (n=1; 5.89%), venlafaxine (n=1; 5.89%).

Validation design and statistical methods

The DID-W1 was tested as to the inter-rater agreement requirement. It was administered by 2 raters independently assessing the same patient in different times of the same day. This is the most customary way of assessing observer variability that may arise from differences in input, procedure, or users.

Percent agreement and Cohen's kappa were used to measure inter-rater reliability. Percent agreement is directly interpreted as the percent of data that are correct. Cohen's kappa (κ), a robust statistic for inter-rater testing, is a form of correlation coefficient which cannot be directly interpreted, but a squared correlation coefficient, called the coefficient of determination is directly interpretable[38]. Similar to correlation coefficients, kappa can range from −1 to +1, where 0 represents the amount of agreement that can be expected from random chance, and 1 represents perfect agreement between the raters. Cohen suggested the kappa result be interpreted as follows: ≤0 no agreement; 0.01-0.20 none to slight; 0.21-0.40 fair; 0.41-0.60 moderate; 0.61-0.80 substantial; 0.81-1.00 almost perfect agreement[39].

Table 2. First row of module DID-W1-WS1, section a.

Current new withdrawal symptoms	Diagnostic criteria[9]	Answer	Instruction for the interviewer
After the last dose reduction or discontinuation of (name of the drug), has there been a period of time when you have had symptoms that you did not have before, except in previous attempt to reduce or discontinue a psychotropic medication? If **yes** would you relate them to dose reduction or discontinuation of (name of the drug)?	*(B) One or more of the following symptoms: nausea, headaches, tremor, sleep disturbances, decreased concentration, anxiety, irritability, agitation, aggression, depression, or dysphoria*	☐ Yes ☐ No	*if **yes** to both questions, code yes* *if **no**, code no in the box at the end of section 1A and go to section 1B*

We designed the DID-W1, the first diagnostic interview for identifying and differentiating drug withdrawal. It was based on the new diagnostic criteria proposed by Chouinard & Chouinard[9] taking as model the withdrawal syndromes associated with all psychotropic drugs including narcotics, hypnotics, anxiolytics, and drugs given in medicine to treat for example high blood pressure[25]. This semi-structured clinical interview aims at formulating the diagnosis of new symptoms, rebound, and persistent postwithdrawal disorders according to the diagnostic criteria by Chouinard & Chouinard[9]. This is the first study testing the psychometric properties of the DID-W1, inter-rater reliability results are here presented.

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RESULTS

The percent agreement for the whole interview was 97.06%, the Cohen's kappa was 0.85 (SE=0.083) with a 95% CI of 0.61-1.08, the squared correlation coefficient was 0.72. Inter-rater concordance was excellent. Table 3 reports the percent agreement, the Cohen's kappa with 95% CI, and the squared correlation coefficient for each diagnosis.

DISCUSSION

A kappa value above 0.80 indicates excellent inter-rater agreement and suggests that the DID-W1 is a reliable method for diagnostic evaluation in SSRI/SNRI withdrawal syndromes.

This is the first tool designed to identify and classify the various clinical manifestations that are associated with SSRI and SNRI discontinuation, according to Chouinard & Chouinard's[9] diagnostic criteria. The most widely used method for assessing such phenomena has been for a long time the Discontinuation Emergence Signs and Symptoms (DESS)[40], a checklist of signs and symptoms of withdrawal with no diagnostic purposes, even though the patients may be classified as experiencing a withdrawal syndrome if the number of DESS checklist events increased by four or more during the discontinuation period.

The DID-W1 is an interview which may have a number of important clinical and research implications. First, it is a tool for identifying and differentiating the clinical phenomena that may occur upon SSRI and SNRI discontinuation. Not surprisingly, there is a wide variation (between 14 and 78%) on the incidence of withdrawal symptoms after dose reduction, discontinuation, or switch of SSRIs or SNRI[9,41]. It may depend on drug differences and on the samples that are studied, but also on the lack of suitable diagnostic instruments. Second, it may help differentiating withdrawal phenomena from relapse[9,42]. In clinical practice, lack of appraisal of withdrawal phenomena may lead to inappropriate clinical decisions, such as unnecessary re-institution of drug treatment. In research, it may allow to differentiate between withdrawal phenomena and relapse after antidepressant discontinuation, which would otherwise be impossible to discern[43]; it may yield a full assessment of side effects of antidepressant drugs[41]; it may lead to a correct identification of distress and use of antidepressants in epidemiological studies[44]. Finally, psychiatric symptoms in clinical practice may also be a consequence of previous pharmacological treatments, the so called iatrogenic comorbidity, that would require removal of the drug but is more often interpreted as a justification for new treatment[11]. For instance, much of the refractoriness to treatment of anxious depression may be actually due to post-withdrawal disorders that are secondary to the use of antidepressant drugs in anxiety disorders[45]. Such research efforts pertain to the domains of clinical pharmacopsychology, an emerging area that is concerned with the subtle psychological modification induced by psychotropic and medical drugs, with particular reference to behavioral toxicity and iatrogenic comorbidity[46,47].

It is hoped that the DID-W1 will encourage studies on this topic and may lead to a refinement of patients' assessment, as well as treatment, in clinical settings. There is however the need for other reliability studies on the DID-W1 such as comparisons with the DESS as well as construct validity studies. There is also need of similar semi-structured interviews to be produced for classifying withdrawal syndrome related to other drugs, such as antipsychotics[25].

Table 3. Inter-rater reliability per diagnosis.

	% of agreement	Cohen's kappa (SE)	95%CI	Squared correlation coefficient
Current new withdrawal symptoms	100.00	1.00 (0.00)	-	1
Lifetime new withdrawal symptoms	88.23	0.72 (0.18)	0.15-1.29	0.51
Current rebound withdrawal symptoms	100.00	1.00 (0.00)	-	1
Lifetime rebound withdrawal symptoms	94.11	0.63 (0.33)	-0.34-1.60	0.40
Current persistent post-withdrawal disorder	100.00	1.00 (0.00)	-	1
Lifetime persistent post-withdrawal disorder	100.00	1.00 (0.00)	-	1

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