

# The Emerging Role of Clinical Pharmacopsychology

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## Abstract

**Background:** Clinical pharmacopsychology is an area of clinical psychology that is concerned with the application of clinimetric methods to the assessment of psychotropic effects of drugs on psychological functioning, and the interaction of such drugs with specific or non-specific treatment ingredients. Clinical pharmacopsychology derives its data from observational and controlled studies on clinical populations and refers to the therapeutic use of medical drugs, not to the effects of substances used for other purposes.

**Method:** Domains and operational settings of clinical pharmacopsychology are illustrated.

**Results:** The domains of clinical pharmacopsychology extend over several areas of application which encompass the psychological effects of psychotropic drugs (with particular emphasis on subclinical changes), the characteristics that predict responsiveness to treatment, the vulnerabilities induced by treatment (i.e., side effects, behavioral toxicity, iatrogenic comorbidity), and the interactions between drug therapy and psychological variables. A service for clinical pharmacopsychology is here proposed as an example of the innovative role of clinical psychology in medical settings.

**Conclusion:** Clinical pharmacopsychology offers a unifying framework for the understanding of clinical phenomena in medical and psychiatric settings. Its aim is to provide a comprehensive assessment of the clinical important changes that are concerned with wanted and expected treatment effects; treatment-induced unwanted side effects; and the patient's own personal experience of a change in terms of well-being and/or quality of life. It is now time to practice clinical pharmacopsychology, creating ad hoc services in Europe.

## Keywords

clinical pharmacopsychology, antidepressant drugs, psychotropic medication, clinical service, psychopharmacology



## Highlights

- Clinical pharmacopsychology assesses the effects of medications on psychological functioning
- Since clinical psychologists visit medicated patients, a comprehensive clinical evaluation is crucial
- Vulnerabilities induced by psychotropic drugs are an important area of application of clinical pharmacopsychology

The term “pharmacopsychology” was introduced by Kraepelin to indicate the effects of medical drugs on psychological functioning (Kraepelin, 1892). He thought it was important to describe the psychological changes induced by pharmacotherapy. Later, Pierre Pichot edited a volume of psychological measurements in psychopharmacology (Pichot, 1974) outlining new needs that derived from measuring the changes induced by psychotropic medications. Two categories of instruments were collected by Pichot (Pichot, 1974) for psychometric measurement in psychopharmacology: self-rating instruments (e.g., the Hopkins Symptom Checklist - HSCL) (Derogatis, Lipman, Rickels, Uhlenmuth, & Covi, 1974) and clinician-reported rating scales (e.g., the Hamilton Depression Scale) (Hamilton, 1974). Over time, experimental pharmacopsychology was also defined, thus contributing to differentiate pharmacopsychology from psychopharmacology and introducing psychology into the clinical and psychiatric field (Eysenck, 1963; Janke, 1983; Janke, Debus, & Erdmann, 2000; Janke & Netter, 2004; Lipton, Di Mascio, & Killam, 1977).

The term “clinical pharmacopsychology” has been introduced to indicate the clinical psychology approach to pharmacology (Fava, Tomba, & Bech, 2017). Clinical pharmacopsychology was defined as the application of clinimetric methods to the assessment of psychotropic effects of medications, and the interaction of drugs with specific and non-specific treatment ingredients (Fava, Tomba, & Bech, 2017). It should be differentiated from the approach of experimental psychology to pharmacology, i.e., experimental pharmacopsychology. Clinical pharmacopsychology derives its data from observational and controlled studies on clinical populations, whereas experimental pharmacopsychology derives its data mainly from the laboratory and does not necessarily involve clinical populations. Clinical pharmacopsychology refers to the therapeutic use of medical drugs and should be differentiated from the study of the effects of substances used for other purposes (Fava, Tomba, & Bech, 2017).

In experimental psychology the distinction between pharmacopsychology and psychopharmacology is very clear. Pharmacopsychology is defined as the use of drugs as tools to discover or explain psychological functions or to detect differences in drug responsiveness, mostly in healthy persons serving as models for psychiatric diseases (Eysenck, 1963; Janke, 1983; Janke, Debus, & Erdmann, 2000) while psychopharmacology

is defined as the discipline investigating psychological effects of drugs usually in clinical groups; it also includes treatment prediction, drug responsiveness and side effects, always in the context of clinical investigations (Lipton, Di Mascio, & Killam, 1977).

An essential characteristic of clinical pharmacopsychology is that it refers to a clinimetric, instead of a psychometric, conceptual model. Clinimetrics has a set of rules which governs the structure of indices, the choice of component variables, the evaluation of consistency and validity, and differs from classical psychometrics (Bech, 2016; Fava, Tomba, & Sonino, 2012; Feinstein, 1987). An essential clinimetric requisite for an assessment method is its discrimination properties (i.e., responsiveness/sensitivity), which means that the tool should be able to detect clinically relevant changes in health status over time (Fava, Tomba, & Bech, 2017). Just as important is incremental validity which refers to the unique contribution (or incremental increase) in predictive power associated with a particular assessment procedure in the clinical decision process (Fava, Rafanelli, & Tomba, 2012).

We will here describe the most important domains which pertain to clinical pharmacopsychology and propose a setting for clinical pharmacopsychology.

## Domains of Clinical Pharmacopsychology

The domains of clinical pharmacopsychology extend over several areas of application which encompass the psychological effects of psychotropic drugs, the characteristics that predict responsiveness to treatment, the vulnerabilities induced by treatment (i.e., side effects, behavioral toxicity, iatrogenic comorbidity), and the interactions between drug therapy and psychological variables.

### Psychological Effects of Psychotropic Drugs

In 1968, DiMascio and Shader criticized the tendency “to select, from among the many pharmacologic actions that a drug may possess, a specific effect to consider as the main (therapeutic or beneficial) effect and to describe all others as side-effects” (DiMascio & Shader, 1968, p. 617). They noted that a drug effect such as sedation or motor stimulation may be considered adverse for one patient, and yet therapeutic and desired for another one. Similarly, within the same patient it may be of value at one stage of an illness and adverse at a later stage.

In clinical trials, a limited number of symptoms is usually selected to test efficacy and psychological measurements are targeted. These pragmatic needs have limitations since excessive reliance on symptoms that are part of diagnostic criteria of mental disorders (e.g., major depressive disorder and generalized anxiety disorder) has impoverished clinical assessment.

Indices may be observer-rated or self-rated. While observer-rated methods make full use of the clinical experience and comparison potential of the interviewer, self-rating methods allow a more direct assessment of the patient's subjective perceptions. For instance, when the aim is to assess quality of life, research in this area seeks essentially two kinds of information: the functional status of the individual and the patient's appraisal of their own health. Indeed, the subjective perception of health status (e.g., lack of well-being, demoralization, difficulties fulfilling personal and family responsibilities) is as valid as that of the clinician in evaluating outcomes (Bech, 1990; Topp, Østergaard, Søndergaard, & Bech, 2015). The emphasis on patient-reported outcomes, any report coming directly from patients about how they function or feel in relation to a health condition or its therapy (Clancy & Collins, 2010), is in line with this conceptualization.

An interesting example of standard assessment of psychological effects of antidepressant drugs can be found in placebo-controlled studies which observed that antidepressants decrease reactivity to social environment in depressed patients as assessed by the Clinical Interview for Depression (Guidi, Fava, Bech, & Paykel, 2011). The decrease may certainly be beneficial in an acute depressive state. However, it is conceivable, even though yet to be adequately investigated, that in a residual phase the same effect may entail apathy (Rothschild, Raskin, Wang, Marangell, & Fava, 2014). To ascertain this, however, one needs to rate reactivity to environmental stimuli and apathy, something that is omitted in standard clinical trials (Guidi et al., 2011; Rothschild et al., 2014). Further, high sensitivity is required for detecting residual symptomatology, which was found to characterize most of the patients who were judged to be remitted according to the DSM criteria and no longer in need of active treatment (Fava, Rafanelli, & Tomba, 2012). Excessive reliance on symptoms that are part of diagnostic criteria of mental disorders (e.g., major depressive disorder, generalized anxiety disorder) does not reflect the broad spectrum of variables that affect clinical presentations: subclinical distress (Fava, Rafanelli, & Tomba, 2012), such as demoralization and irritable mood (Fava, Cosci, & Sonino, 2017), psychological well-being and euthymia (Fava & Bech, 2016), mental pain (de Leon, Baca-Garcia, & Blasco-Fontecilla, 2015; Verrocchio et al., 2016), social adjustment (Bech, 2005) and neuroticism (Tyrer, Tyrer, & Guo, 2016).

## Likelihood of Responsiveness

Richardson and Doster (2014) underscored that, in the process of evidence-based decision, one should include: 1. *baseline risk* of poor outcomes from an index disorder without treatment, which is important to identify if the treatment produced benefits; 2. *responsiveness* to the treatment option, which is important to verify if remission has been obtained; 3. *vulnerability* to the adverse effects of treatment, which is important to verify if the treatment triggered an iatrogenic comorbid disorder or if the treatment caused reversible or irreversible side effects.

The likelihood of responsiveness to a certain drug treatment and the clinical characteristics that predict response are a crucial issue in psychopharmacology, even though, in recent years, excessive emphasis on the treatment of the average patient has decreased interest in these aspects (Bech, 2016; Fava, 2017; Richardson & Doster, 2014).

While there is a clinical need to have the broadest picture of the effects of a drug, determination of responsiveness may be based on selected items (Bech, 2016). In addition, it has become common practice in clinical trials to quantify the number of participants who, after a pharmacologic and/or psychotherapeutic trial, achieve response or remission according to specific cut-off points of rating scales (Guidi et al., 2018). Remission can be expressed either as a categorical variable (e.g., present/absent) or as a comparative category (e.g., non-recovered, slightly recovered, moderately recovered, or greatly recovered) which refers to the clinical distance between the current state of the patient and his pre-treatment position (Bech, 1990). This method of research has limitations and makes difficult the translation of the research results into practice. For instance, an improvement according to specific cut-off points of rating scales might not mirror a real clinical improvement of the patients as it is perceived by the patient or observed by the clinician.

In the same vein, many studies are concerned with relapse and recurrence as primary outcome measures, even though adequate criteria are not available for all mental health conditions and clinicians and researchers in clinical psychiatry often confuse response to treatment for full recovery (Bech, 1990; Fava, 1996).

Finally, where differentiation according to cogent subgroups is made in clinical trials, a treatment which is helpful on average in the average patient might be ineffective in some patients (i.e., no difference with placebo) and even harmful in someone else (i.e., worse than placebo) (Horwitz, Hayes-Conroy, & Singer, 2017; Horwitz, Singer, Makuch, & Viscoli, 1996).

In this framework, clinimetrics can offer an accurate method to measure responsiveness to a treatment. This method is based on staging an assessment of the longitudinal development and of the longitudinal rollback of mental disorders (Cosci & Fava, 2013). Staging differs from the conventional diagnostic practice in that it does not only define the extent of progression of a disorder at a particular point in time but also where a person is currently along the continuum of the course of illness. Staging defines prodromes (e.g., early symptoms and signs that differ from the acute clinical phase) and residual symptoms (e.g., persistent symptoms and signs despite apparent remission or recovery). More specifically, Stage 1 is the prodromal phase -that is the time interval between the onset of prodromal symptoms and the onset of the characteristic manifestations of the fully developed illness (Cosci & Fava, 2013). After the acute phase (Stage 2), it might be difficult to assess whether partial or full remission has occurred, and attenuated symptoms, the so-called residual symptoms, might be observed (Stage 3); they are due to partial persistence of the disorder or an aggravation of a pre-existing abnormal personality trait. Stage 4 represents chronicity of the psychiatric disorder (Cosci & Fava, 2013).

There appears to be a relationship between residual and prodromal symptoms. [Detre and Jarecki \(1971\)](#) provided a model defined as the rollback phenomenon: as the illness remits, it progressively recapitulates, albeit in reverse order. Certain prodromal symptoms may be overshadowed by the acute manifestations of the disorder, but they persist as residual symptoms and progress to become prodromes of relapse. Prodromal symptoms of relapse tend to mirror, in fact, those of the initial episode ([Cosci & Fava, 2013](#)). According to the rollback model, there is also a temporal relationship between the time of development of a disorder and the duration of the phase of recovery. This has several exemplifications in clinics. For instance, the persistence of residual symptoms after an antidepressant treatment administered to treat a major depressive episode represents a risk of relapse which should be considered by clinicians and considered as a partial response to the antidepressant treatment administered ([Tomba & Fava, 2012](#)).

## Assessing Side Effects

Evidence Based Medicine is focused on the potential benefits that therapy may entail as to baseline risk, but it is likely to neglect, in addition to responsiveness, also vulnerabilities ([Fava, 2017](#); [Richardson & Doster, 2014](#)). A rational approach to treatment considers the balance between potential benefits and adverse effects applied to the individual patient ([Fava, 2017](#); [Vandenbroucke & Psaty, 2008](#)). The achievement of such balance is hindered by the difficult integration of different sources of information.

Several side effects of psychotropic medications are transient and may disappear after a few weeks following treatment initiation, but potentially serious adverse events may persist or ensue later. Antidepressants' side effects encompass gastrointestinal symptoms (e.g., nausea, diarrhea, gastric bleeding, dyspepsia), hepatotoxicity, weight gain and metabolic abnormalities, cardiovascular disturbances (e.g., heart rate, QT interval prolongation, hypertension, orthostatic hypotension), genitourinary symptoms (e.g., urinary retention, incontinence), sexual dysfunction, hyponatremia, osteoporosis and risk of fractures, bleeding, central nervous system disturbances (e.g., lowering of seizure threshold, extrapyramidal side effects, cognitive disturbances), sweating, sleep disturbances, affective disturbances (e.g., apathy, switches, paradoxical effects), ophthalmic manifestations (e.g., glaucoma, cataract) and hyperprolactinemia ([Carvalho, Sharma, Brunoni, Vieta, & Fava, 2016](#)).

Long-term use of antidepressants such as Serotonin Selective Reuptake Inhibitors (SSRI) may induce weight gain, after an initial period characterized by reduced appetite, and the increased weight does not necessarily recede upon the drug discontinuation ([Carvalho et al., 2016](#)). It has been suggested that an increase in exposure to antidepressants via a multitude of mechanisms may be a driving force for the obesity pandemic ([Lee, Paz-Filho, Mastronardi, Licinio, & Wong, 2016](#)). Similarly, the prevalence of sexual side effects can be as high as 50-70% among individuals taking SSRIs and such effects

may persist even after discontinuation (Carvalho et al., 2016), the so-called post-SSRI sexual dysfunction (Bala, Nguyen, & Hellstrom, 2018).

Negative effects may also occur as a result of psychotherapeutic treatment, whether due to technique, patient or therapist variables, or inappropriate use (Barlow, Gorman, Shear, & Woods, 2000; Linden, 2013; Scott & Young, 2016). The side effects of psychotherapy are difficult to recognize because of the number of variables involved, including the various stages of the psychotherapeutic process (Linden, 2013).

Targets of assessment have predominantly involved the desired effects of a medication while the evaluation of adverse events has been often neglected, although they can be measured via both interviews and self-rated instruments. Assessing the side effects that occur with any type of drug treatment requires a careful clinimetric collection of symptoms in addition to medical laboratory and investigational methods. The UKU side effect rating scale (Lingjærde, Ahlfors, Bech, Dencker, & Elgen, 1987) is an example of scale that considerably improved the detection of side effects, because of its comprehensive nature. For instance, sexual side effects are common and yet are some of the most under-reported adverse effects associated with the use of antidepressants, and a growing body of evidence indicates that such side effects should be monitored by use of specific instruments (Balon & Segraves, 2008; Carvalho et al., 2016). Further, Karch and Lasagna (1975) noted that the history of toxicology reminds us vividly of the lag that often occurs between the first introduction of a drug into humans and the recognition of certain adverse events from that drug. There is a need to update specific instruments for side effects with findings that may derive from case reports and clinical observations. For instance, the wide range of side effects that may ensue with long-term treatment with second generation antidepressants (Carvalho et al., 2016) would require specific methods of investigation.

## Behavioral Toxicity

In 1968, DiMascio and Shader provided a conceptual framework for behavioral toxicity of psychotropic drugs and defined behavioral toxicity as the pharmacological actions of a drug that, within the dose range in which it has been found to possess clinical utility, may produce alterations in mood, perceptual, cognitive, and psychomotor functions, which limit the capacity of the individual or constitute a hazard to his well-being (DiMascio & Shader, 1968). In 1980, Perl and colleagues pointed out that psychotropic drugs can cause behavioral toxicity through the extension of their primary therapeutic action and/or the onset of secondary actions as well as withdrawal, dependence, and tolerance symptoms (Perl, Hall, & Gardner, 1980).

The concept of behavioral toxicity encompasses adverse events that may be limited to the period of drug administration and/or persist long after their discontinuation. Any type of psychotropic drug treatment, particularly after long-term use, may increase the risk of experiencing additional psychopathological problems that do not necessarily sub-

side with discontinuation of the drug or of modifying responsiveness to subsequent treatments (Fava, Cosci, Offidani, & Guidi, 2016). These latter phenomena can be subsumed under the rubric of iatrogenic comorbidity (Fava et al., 2016).

“Iatrogenic comorbidity” refers to unfavorable modifications in the course, characteristics, and responsiveness of an illness that may be related to treatments administered previously (Fava et al., 2016). Such vulnerabilities may occur during treatment administration and/or manifest themselves after its discontinuation. The changes can be persistent and not limited to a short phase, such as in the case of withdrawal reactions, and cannot subsume under the generic rubrics of adverse events or side effects.

Behavioral toxicity may ensue with any type of medical drug. Examples related to antidepressant drug use may be the onset of suicidality and aggression, switching from unipolar to bipolar course, withdrawal phenomena upon discontinuation, post-withdrawal persistent disorders (Carvalho et al., 2016; Fava et al., 2016). Such phenomena require adequate clinimetric indices for their detection, as the late recognition of withdrawal syndromes after antidepressant discontinuation teaches (Chouinard & Chouinard, 2015).

Behavioral toxicity may apply also to drugs directed to medical conditions (Shader, 1972; Tisdale & Miller, 2010; Whitlock, 1981), which may induce depression, anxiety, and other psychiatric symptoms.

Examples of behavioral toxicity that are concerned with the use of antidepressant drugs encompass switching into mania or hypomania during treatment, both in bipolar disorder (Tondo, Vázquez, & Baldessarini, 2010) and in allegedly unipolar patients (Joseph, Youngstrom, & Soares, 2009; Offidani, Fava, Tomba, & Baldessarini, 2013); withdrawal symptoms following reduction or discontinuation of antidepressant treatment, in the form of acute withdrawal symptomatology or persistent post-withdrawal disorders (Chouinard & Chouinard, 2015). Such manifestations of behavioral toxicity may be easily misinterpreted as a sign of impending relapse or the need to keep the antidepressant at the same dosage. Untreated symptoms may be mild and resolve spontaneously in one to three weeks; in other cases, they may persist for months or even years (Chouinard & Chouinard, 2015). Their prevalence is unknown at the moment, due to their very recent definition. The high prevalence of mental disorders in the general population may also be an effect of the presence of disorders that are a consequence of previous pharmacological treatments (Cosci, Guidi, Balon, & Fava, 2015). For instance, much of the refractoriness to treatment of anxious depression may be actually due to persistent post-withdrawal disorders that are secondary to the use of antidepressant drugs in anxiety disorders (Fava & Tomba, 2014).

All these phenomena may be explained based on the oppositional model of tolerance. Continued drug treatment may recruit processes that oppose the initial acute effect of a drug. When drug treatment ends, these processes may operate unopposed, at least for some time and increase vulnerability to relapse (Fava & Offidani, 2011).

## Interaction of Medical Drugs With Behavioral Variables and Psychotherapy

Each therapeutic act may be a result of multiple ingredients that can be specific or non-specific: expectations, preferences, motivation, illness behavior and patient-doctor interactions are examples of variables that may affect treatment outcome (Fava, Guidi, Rafanelli, & Rickels, 2017; Rickels, 1968; Schedlowski, Enck, Rief, & Bingel, 2015). Such variables may be the object of study of clinical pharmacopsychology.

In 1969, Uhlenhuth, Lipman, and Covi examined the combinations of pharmacotherapy and psychotherapy in psychiatric disorders. They outlined four models of interaction: a) addition (i.e., the effects of two interactions combined equals the sum of their individual effects); b) potentiation (i.e., the effect of two interventions combined is greater than the sum of their individual effects); c) inhibition (i.e., the effect of two interventions combined is less than each individual effect); d) reciprocation (i.e., the effect of the two interventions combined equals the individual effect of the more potent intervention). Most of the studies are compatible with the additive and reciprocal concepts of interaction (Cuijpers et al., 2014; Forand, de Rubeis, & Amsterdam, 2013; Guidi et al., 2018; Uhlenhuth et al., 1969). There are, however, some high quality and well-designed individual studies suggesting that addition of a benzodiazepine or an antidepressant to cognitive behavioral treatment of anxiety disorders could be detrimental compared to placebo at follow-up (Barlow et al., 2000; Haug et al., 2003; Marks et al., 1993; Nordahl et al., 2016), thus indicating an inhibitory effect of the interaction. Again, clinical pharmacopsychology could be crucial for disclosing the nature of these relationships.

## The Setting for Clinical Pharmacopsychology

We illustrate here a Clinical Pharmacopsychology Service as an example of an innovative application of clinical psychology in the medical setting.

### A Clinical Pharmacopsychology Service

The Service has been operating since 2018 at the Department of Health Sciences, University of Florence (Florence, Italy). This outpatient clinic is addressed to patients who are looking for treatment programs allowing to rationalize, reduce, and discontinue psychotropic medications. The Service is run by an experienced clinical psychologist from the University of Florence who has a special interest and training in psychopharmacology, psychotherapy, and psychosomatic medicine. The outpatient facility is open one day a week with space for a maximum of eight patients and at least one hour dedicated to each patient.

The clinical psychologist works jointly with two psychologists (providing psychotherapy) and two consultants (one internist and one psychiatrist with a strong back-

ground in psychopharmacology). The clinical psychologist makes the initial assessment and monitors treatment choices. Team members work in close coordination, with repeated assessments and sequential combination of treatments (Fava, Park, & Dubovsky, 2008).

The main source of referral is the webpage<sup>1</sup> of the Service that was created to disseminate knowledge on the clinical phenomenon of withdrawal after discontinuation of antidepressants. Usually, the patients already looked for an aide in their environment (e.g., the psychiatrist or the general practitioner who prescribed the medication) without success before asking for an aide at the Service.

The first visit at the Service is conducted as follows, although the order of the schedule could be changed as required:

- complete history of psychiatric/psychological aspects according to the principles of macro-analysis (see below);
- formulation of the case, also on the basis of clinimetric tools (Fava, Tomba, & Sonino, 2012, Fava, Rafanelli, & Tomba, 2012), staging (Cosci & Fava, 2013), subtyping of diagnostic categories (see below);
- in addition to psychiatric diagnoses according to the DSM, the patient is evaluated via the Diagnostic clinical Interview for Drug Withdrawal 1 (DID-W1) (Cosci, Chouinard, Chouinard, & Fava, 2018) and the Discontinuation-Emergent Signs and Symptoms (DESS) (Rosenbaum, Fava, Hoog, Ascroft, & Krebs, 1998) (see below);
- the clinical psychologist goes over the patient's documents and previous workup;
- appraisal of the present situation, based on all findings (including answers to the DID-W1 and the DESS) and patient education;
- discussion of treatment choices and prescriptions.

The Diagnostic clinical Interview for Drug Withdrawal 1 (DID-W1) – New Symptoms of Selective Serotonin Reuptake Inhibitors (SSRI) or Serotonin Norepinephrine Reuptake Inhibitors (SNRI) is a semi-structured interview assessing withdrawal syndromes according to Chouinard's diagnostic criteria (Cosci et al., 2018). Such criteria identify three different withdrawal syndromes: new withdrawal symptoms, rebound syndrome, and persistent post-withdrawal disorder. The Discontinuation-Emergent Signs and Symptoms (DESS) is a self-administered checklist of signs and symptoms which might occur after the discontinuation of SSRI.

We will give an exemplification of this approach with the following case.

## The Case of Miss X.

In order to illustrate, in practice, the activities at the Service of Pharmacopsychology, we present a clinical case.

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1) <https://www.smettereglipsofarmaci.unifi.it/changelang-eng.html>

Miss X. came to our attention after having been visited by several psychiatrists who suggested she should maintain paroxetine, which had been prescribed 10 years earlier for a panic disorder diagnosis. She received this suggestion each time she tried to reduce paroxetine and had the occurrence of anxiety, panic attacks, and depressed mood.

At first visit, the patient did not satisfy DSM diagnostic criteria for psychiatric disorders. She was strongly determined to reduce paroxetine for the following reasons: she gained about 10 kilograms of weight in 10 years, she had dampened sexual desire, she had mild hyperglycaemia and she did not want to live with paroxetine any longer.

The clinical psychologist performed the macro-analysis (Fava & Tomba, 2014; Tomba & Fava, 2012), which allows to establish a relationship between co-occurring syndromes and problems based on where treatment should begin in the first place and assuming that there are functional relationships among problematic areas and that the targets of treatment may vary during the course of disturbances. For Miss X., the problematic areas were: past attempts to reduce paroxetine which invariably produced the reappraisal of anxiety, panic attacks, depressed mood, and failure to discontinue paroxetine weight gain; hyperglycaemia and sexual dysfunction.

Thereafter, microanalysis, a detailed analysis of symptoms for functional assessment (Emmelkamp, Bouman, & Scholing, 1993), was performed. It requires consideration of the onset of complaints, their course, circumstances that aggravate or ameliorate symptoms, short-term and long-term impact of symptoms on quality of life, and work and social adjustment (Emmelkamp et al., 1993), and may include specific tests and rating scales (Bech, 1993) which must be integrated into the rest of the assessment and not viewed in isolation (Emmelkamp et al., 1993). In the framework of the micro-analysis, both DESS and DID-W1 were proposed to Miss X. The DESS did not provide additional information. The DID-W1 disclosed that the patient met the criteria for past rebound syndrome. Thus, the problematic areas in the macro-analysis were updated as follows: past attempts to reduce paroxetine which failed; lifetime rebound syndromes; weight gain; hyperglycaemia and sexual dysfunction.

On the basis of the macro- and the micro-analysis, the clinical psychologist asked for the consultation of the internist and the psychiatrist. It was decided to taper and discontinue paroxetine. The aim was to limit weight gain, help to normalize the hyperglycaemia (probably due to an excessive intake of carbohydrates) and verify whether paroxetine discontinuation improved sexual dysfunction. The clinician deferred to a second stage assessment the determination of whether paroxetine reduction triggers a withdrawal syndrome (Chouinard & Chouinard, 2015).

At a second visit, which occurred eight days later and seven days after the reduction of paroxetine from 40 mg to 35 mg daily, Miss X. presented also anxiety and mood swings. The clinical psychologist ran again the macro- and micro-analysis, administered again DID-W1 and DESS and updated the problematic areas as follows: past attempts to reduce paroxetine which failed; lifetime rebound syndromes; weight gain; hyperglycae-

mia; sexual dysfunction; current rebound syndrome characterized by anxiety and mood swings. Via the diagnosis of rebound syndrome the clinician was able to subtype and differentiate within the broader diagnostic entity of withdrawal syndrome. At re-assessment, the clinical reasoning was also used and let the clinical psychologist go through a series of “transfer stations” where potential connections between presenting symptoms and pathophysiological process are drawn (Feinstein, 1973). Based on the re-assessment as well as on the clinical reasoning, the clinical psychologist proposed Miss X. the psychotherapeutic management suggested by Fava and Belaise (2018).

## Accomplishments and Shortcomings

In brief, the assessment provided to patients incorporates variables such as type and duration of psychotropic medication treatment, patterns of symptoms, stage of illness, comorbid conditions, timing of phenomena, responses to previous attempts to discontinue, and other clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same diagnosis and the same drug treatment. Such variables are filtered by the clinical judgment (Fava & Tomba, 2014; Tomba & Fava, 2012) which provides the following assessment strategies: the use of diagnostic transfer stations instead of diagnostic end-points using repeated assessments, subtyping versus integration of different diagnostic categories, staging, macro- and micro-analysis (Fava, Rafanelli, & Tomba, 2012). During the treatment path, patients are reassessed after the first line of treatment has been completed to reconfirm the diagnosis and refine the treatment plan.

This service fills gaps that are left with ordinary psychiatric care, and provides a comprehensive assessment which goes beyond the DSM and includes clinimetric tools.

Of course, difficulties might emerge from a comprehensive assessment of this kind. At least two main practical issues should be raised. The first is that it is not easy to have these kinds of services as part of the national health system which commonly imposes a time constraint of 15-20 minutes per visit. Second, there is an economic load for the national health system or for the patient due to the high level of engagement of clinicians. However, if we use a medium/long-term perspective, we may see that the cost is only apparently high since the patients in the majority of cases stop medications and maintain a symptoms-free condition without needing further visits in future years.

Finally, a potential shortcoming of the service is that it does not cooperate with a laboratory which monitors drug blood levels which could be related to psychological withdrawal or treatment responses.

## Conclusions

Clinical pharmacopsychology offers a unifying framework for the understanding of clinical phenomena in medical and psychiatric settings (Fava, Tomba, & Bech, 2017). Its domains encompass the clinical benefits of psychotropic drugs, the characteristics that predict responsiveness to treatment, the vulnerabilities induced by treatment (i.e., side effects, behavioral toxicity, iatrogenic comorbidity), and the interactions between drug treatment and psychological variables. Its aim is to provide a comprehensive assessment of the clinically important changes that are concerned with wanted and expected treatment effects; treatment-induced unwanted side effects; and the patient's own personal experience of a change in terms of well-being and/or quality of life. It is now time to practice clinical pharmacopsychology, creating ad hoc services in Europe.

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