Treatment non-response in OCD: methodological issues and operational definitions

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Abstract

While controlled trials with SRIs have demonstrated a selective efficacy in obsessive–compulsive disorder (OCD), up to 40–60% of patients do not have a satisfactory outcome. Non-response to treatment in OCD is associated with serious social disability. There are a large number of non-responsive patients, and they are difficult to cluster due to ambiguities in the diagnostic criteria, possibility of subtypes, and a high rate of comorbidity. Moreover, the findings of current studies of so-called 'non-responsive' cases are currently non-generalizable because of the lack of an operational definition of non-response. The result has been that a cumulative body of data on a reasonably homogeneous sample of non-responders has not been developed. The aims of this paper are to clarify some of the obstacles in defining stages of response and levels of non-response and, through a comprehensive analysis, to propose a systematic nosology for this rather common condition. Better characterization of which patients respond and do not respond to various treatments will enable more accurate clustering of patients, and help facilitate multi-site data collection for future research trials.

Introduction: non-response is a clinical challenge and theoretical puzzle

While controlled trials with SRIs have demonstrated a selective efficacy in obsessive–compulsive disorder (OCD), up to 40–60% of patients do not have a satisfactory outcome (CMI, 1991; Goodman et al., 1992; Jenike and Rauch, 1994; McDougle et al., 1993b; Piccinelli et al., 1995; Pigott and Seay, 1999; Rasmussen et al., 1993) and these patients have significant disability and morbidity (Hollander et al., 1996). Since there is no operational definition for the concept of 'non-response', the labels 'non-responder', 'treatment-resistant', and 'treatment-refractory' are often used idiosyncratically and synonymously, and all of these terms lack established content validity.

Notwithstanding the lack of precise definitions of response and non-response, several different 'next-step' therapeutic strategies and even more complex treatment algorithms have been proposed (Dominguez, 1992, Dominguez and Mestre, 1994; Goodman et al., 1993; Hollander and Pallanti, 2002; Jefferson et al., 1995; Jenike 1992; March et al., 1997; Rasmussen and Eisen 1997; Rasmussen et al., 1993). An evidence-based medicine approach would recommend that clinicians integrate their individual clinical expertise with the best available evidence from systematic research (Guyatt et al., 1993, 1994, 1999). A clear definition and limits of the different clinical phases of the disorder represent a basic requirement to trace any therapeutic algorithm. However, in OCD treatment studies, the lack of operational criteria for non-response has prevented the development of a cumulative body of data on a reasonably homogeneous sample of 'non-responsive' patients, which has created significant limits on the generalizablity of the few existing studies and remains a significant obstacle in the development of useful new studies.

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By establishing 'stages' of response, a clinician may reliably determine the type of treatment response, and thereby be guided towards a next-step strategy (e.g. continue with the treatment, augment the treatment, change the treatment). By establishing 'levels of non-response', clinicians and researchers may better characterize the subset of patients according to therapeutic history. With standardized criteria in place, patients previously thought to be totally unresponsive (i.e. 'refractory') to treatment may become re-categorized, and patients with well-defined treatment will become more homogenous and comparable across sites.

The aims of this paper are to clarify some of the obstacles in defining stages of response and levels of non-response and, through a comprehensive analysis, to propose a systematic nosology for this rather common condition.

Measures of treatment response: impact on definition of non-response

Response criteria markedly impact the percentage of subjects considered responders in various trials and studies that utilize different response criteria and yield very different response rates. The importance of using standardized clinical rating scales in clinical practice as well as in research studies must be stressed. Treatment response should be assessed qualitatively via periodic clinical interviews and the regular use of validated scales. The Yale–Brown Obsessive Compulsive Scale (Y-BOCS) is the most widely and frequently used instrument to quantify the ongoing severity of OCD symptoms. As approx. 60% of patients treated with SRIs experience at least a 25–35% decrease in symptoms on the Y-BOCS (Goodman et al., 1992), one of these cut-off points has typically been operationalized as the criterion for non-response. In an adequate trial of an SRI, a less than 25% decrease in the Y-BOCS score in patients with at least moderate obsessive–compulsive symptom severity (Goodman et al., 1990) is usually considered partial response or non-response.

Despite the value of the Y-BOCS in measuring symptom severity, it may not be sensitive to subtle changes, such as a decrease from 5 h to 3 h per day of rituals. The Clinical Global Impression (CGI) scale is considered effective in capturing both the larger clinical picture of psychopathology and subtle changes, though it lacks specificity. However, patients with a CGI improvement score of 1 'very much improved' or 2 'much improved' are usually considered responders.

However, when the presence of symptoms does not directly correlate to the severity of disability, it seems questionable to base clinical assessment solely on these two instruments. For instance, no direct correlation exists between the severity of obsessive and compulsive symptoms and severity of distress, especially in the young, where only 1 out of 10 subjects report symptoms to be disturbing (Apter et al., 1996). Subjective well-being is a neglected dimension of assessment, only partially considered in the patient's CGI score.

Quality of life has been a recent focus for OCD studies, using measurement instruments such as the Health Related Quality of Life (HQRL) scale; currently, however, only five studies are available (Koran, 2000). Although no consensus exists on how to conceptualize the HRQL, the importance of considering this dimension of patient suffering is evident. If the presence of symptoms has a substantial negative effect on the HRQL score, this score may be a crucial tool for evaluating the degree of recovery following treatment, and its assessment should be included in the characterization of non-responsive cases. Psychoeducation might play an important role in improving HRQL in resistant OCD patients and needs to be included in the treatment planning.

Goals, terminology, and staging

In considering the definition of non-response, we must first examine our expectations for treatment. Is recovery a reasonable goal of treatment in OCD patients? Some follow-up studies have reported that after many years some individuals with OCD improve independently of the adequacy of treatment (Orloff et al., 1994; Skoog and Skoog, 1999). Currently, the majority of research consists of short-term clinical trials. Leonard et al. (1993) showed that many children and adolescents with OCD no longer meet criteria for the disorder at follow-up. Long-term studies indicate a range of outcomes from full-blown illness to complete remission. For several other disorders, including major depression, a full response in a clinical trial indicates a return to a condition substantially indistinguishable from a healthy control. In OCD, a return to a state of no illness is a rare clinical event.

Episodic course, with a return to a clinical state of no illness, has also been reported in adults (Perugi et al., 1998; Ravizza et al., 1997). An estimated 5% of OCD cases have an episodic course (Rasmussen and Eisen, 1997). Therefore, including 'recovery' and 'remission' in the staging terminology seems reasonable.

Recovery might therefore be considered a realistic target in some patients. Table 1 offers operationalized categories of response to treatment. Since this finding is incompatible with the short-term nature of controlled clinical trials, the duration of both study observations and treatment courses in OCD studies must be re-considered. Additionally, as Orloff et al. (1994) and Skoog and Skoog

Table 1. Stages of response

Stage of response	Stage	Description
I	Recovery	Not at all ill; less than 8 on Y-BOCS
II	Remission	Less than 16 on Y-BOCS
III	Full response	35% or greater reduction of Y-BOCS and CGI 1 or 2
IV	Partial response	Greater than 25% but less than 35% Y-BOCS reduction
V	Non-response	Less than 25% Y-BOCS reduction, CGI 4
VI	Relapse	Symptoms return (CGI 6 or 25% increase in Y-BOCS from remission score) after 3+ months of 'adequate' treatment
VII	Refractory	No change or worsening with all available therapies

(1999) are the only two long-term studies of OCD that have been conducted, new long-term prospective and follow-up studies are needed to better guide our expectations for response.

The authors propose establishment of definitions for treatment response in OCD differentiating between 'recovery' and 'remission', as is proposed by Frank et al. (1991) for depression. We propose *recovery* to indicate an almost complete and objective disappearance of symptoms, corresponding to a Y-BOCS value of 8 or below. *Remission*, on the other hand, can indicate a response that reduces symptoms to a minimal level, a Y-BOCS score of 16 or less, based on this the value is below the minimum threshold value to be included in a clinical trial. Because recovery is supposed to occur only in the episodic course, remission should be considered an adequate term to define the most successful outcome in non-episodic course. Both recovery and remission should be considered the highest levels of response to treatment. Such levels of response are fairly rare, and a lesser response is the more frequent phenomenon. Currently, values of both a 25 and 35% decrease in symptoms in the Y-BOCS total score are typically defined as the criterion for *response* (Goodman and Price, 1982). However, one must address the so-called 'response to recovery issue' (Angst et al., 1996; Fava et al., 1994; Shea et al., 1996; Stahl et al., 2000) that hinges on the definition of the 'appropriate threshold' for response. Stahl (2000) asks, 'Who would accept a 50% reduction of infectious organism for antibiotics, or a 50% reduction of tumour cells in malignancies, as appropriate outcome targets in these other areas of medicine?' As a partial justification for the modest percentage reduction of the Y-BOCS score accepted as 'response', the low placebo response rate (3–5% decrease in Y-BOCS and NIMH global scale scores) has been invoked (Mavissakalian et al., 1985).

We suggest that at least for the purposes of research, a 35% Y-BOCS reduction could reasonably be considered a full response, between 25 and 35% a partial response, and less than 25% a non-response.

Recovery and remission may have to be defined normatively (normative staging), while all the other stages are defined according to the clinical evaluation of the subjective and symptomatic percentage of amelioration in the patient's own context of living (contextual staging).

Furthermore, a recurrence of symptoms should be judged contextually in relation to an individual's previous clinical condition. Considering the peculiarity of OCD, a disorder where the correlation between symptoms and disability is not that strict, an operational definition of episode is required. As with the definition of an episode in depressive disorder (Frank et al., 1991), that of OCD should be defined as a period lasting for at least 2 wk during which a patient is consistently within the fully symptomatic range on a sufficient number of symptoms to meet syndromal criteria for the disorder (Y-BOCS score of 16 or above) and clinical impairment.

A drop in CGI improvement score to '6' ('much worse' or a 25% increase in Y-BOCS from the patient's Y-BOCS score during response) should guide the practitioner toward defining a *relapse*, a term that corresponds with the return of symptoms satisfying the full syndrome during a remission period (return of the symptoms on an ongoing but sub-clinical disorder). *Recurrence* describes an entirely new episode; it thus can occur only during a recovery phase and therefore should apply only to the episodic course presentation of the syndrome.

Maintenance and discontinuation studies (Leonard et al., 1991; Mundo et al., 1997; Pato et al., 1988, 1990) show a high rate of relapse (65–90%) after acute discontinuation of SRI treatment and a lower degree of response to the same treatment effective for the previous episode (Maina et al., 2001). Both the prevalence of partial response and the high percentage of relapse after drug discontinuation make the OCD clinical course similar to that of psychotic disorders (Emsley, 1999). In determining

whether a relapse, exacerbation, or new episode has occurred, the timing of the return of symptoms, during treatment or after discontinuation, is a relevant consideration. It is unclear whether a relapsed OCD patient, following a previous good response to SRI, but with a subsequent non-response, should be considered a 'non-responder'. Negative and partial responses to treatment are operationalized in Table 1. Perhaps a distinction between chronic non-response vs. episodic non-response should also be considered.

Methodological considerations: diagnosis, subtypes, and comorbidity

There are numerous theoretical problems implicit in defining response. Among them are issues centring on the complex relationship between what we assume to be the diagnostic core of a disorder, the limits or boundaries of the disorder, and the impact of treatment outcomes on the evolution of diagnostic classifications. Clearly subtype comorbidity impacts on treatment response and influences our operational definition.

Diagnosis

The concept of non-response suggests an implicit match between a diagnostic classification and a treatment. This match presupposes the validity of diagnostic instruments and categories. While we rely upon the current diagnostic instruments to define clinical entities, these classifications are often treatment-oriented, correlating with the results of 'field trials'. When faced with groups of non-responsive patients, we are forced to question whether the current diagnostic categories hold firm or whether a different constellation should be proposed.

According to conventional traditions of psychopathology, the diagnosis of OCD includes the presence of two clinically distinguishable items: obsession and compulsion. This implies a clear delimitation of both the internal and external boundaries of the terms of definition (Castle and Groves, 2000). The components that make the obsession and compulsion dimensions psychopathological and clearly distinguishable need, however, to be clarified (Leckmann et al., 1997). The distinction between obsessions and other psychopathological entities such as worries (Abramowitz and Foa, 1998) and restricted interests, especially in children (Baron-Cohen and Wheelwright, 1999), needs to be explored further. The boundaries between belief, delusional belief and delusion also present some overlap (Abramowitz and Foa, 1998) and need clarification, as does the importance in the OCD construct of awareness, insight, and the subjective experience of ego-dystonia, which have been marginalized from the diagnosis in the DSM-IV.

These diagnostic issues affect the limits and range of the categorical diagnosis of OCD. As we clarify true non-responders through our exploration of 'matching therapies', current diagnostic boundaries will also need to be reassessed.

Subtypes

Although OCD has long been considered a unitary diagnosis, interest in its potential heterogeneity, as manifested by symptom subgroups, has grown, along with evidence for multidimensionality of OCD symptoms (Summerfeldt et al., 1999).

Onset of illness, particularly with respect to gender differences and age of onset may also be important distinctions in terms of appropriate treatment.

Because reproductive hormones could have specific roles, at least in some specific subtypes such as postpartive onset OCD (Camarena et al., 2001), gender has been suggested as a predictive variable to treatment (Mundo et al., 1999) because brain mechanism in OCD may differ depending on the age at which symptoms are first expressed (Busatto et al., 2001).

Furthermore, late onset could be related to neurological degenerative processes (Weiss and Jenike, 2000), particularly in some at-risk categories of patients, and early onset could be related to a neurodevelopmental process. It also seems reasonable that neuroimaging could be conducted in order to rule out organic aetiology (i.e. post-stroke OCD) before considering an older patient non-responsive to the treatment (Scicutella, 2000).

Another issue concerns the distinction between idiopathic and the so-called 'acquired' OCD (Chacko et al., 2000) with neurological comorbidity such as Huntington's chorea (Scicutella, 2000) and Sydenham's chorea, rheumatic fever, bacterial and viral infection, and encephalitis. This has implications for the possible inclusion of diagnostic or serological examinations in the assessment of suspected cases. Positive findings would also require treatment trials beyond SSRIs before considering patients to be non-responsive. OCD in Tourette's Syndrome, or accompanied by tics, would not be considered non-responsive to only SSRI treatment, but instead be considered inadequately treated without combined typical or atypical neuroleptic treatment (e.g. pimozide, haloperidol, risperidone) (McDougle et al., 2000).

While the predictive negative value of neurological soft signs (Hollander et al., 1990) has been questioned (Thienammen and Koran, 1995), another possible subtype has been suggested from the hypothesis of an immune

Table 2. Levels of non-response

Level of non-response	Description
I	SSRI or CBT
II	SSRI plus CBT
III	2 SSRIs tried plus CBT
IV	At least 3 SSRIs tried plus CBT
V	At least 3 SRIs (including clomipramine) plus CBT
VI	At least 3 SRIs including clomipramine augmentation plus CBT
VII	At least 3 SRIs including clomipramine + CBT + psychoeducation and other classes of medication (benzodiazepine, mood stabilizer, neuroleptic, psycho-stimulant)
VIII	At least 3 SRIs including intravenous clomipramine + CBT + psychoeducation
IX	At least 3 SRIs including clomipramine + CBT + psychoeducation and other classes of antidepressant agents (NSRI, MAOI)
X	All above treatments, neurosurgery

reaction to group A β-haemolytic streptococcal infection, involving anti-neuronal antibodies, in OCD (Swedo et al., 1998). It is yet to be decided whether this type of OCD should be considered a specific subtype, a special pattern of comorbidity, or a new disorder. However, it is clear that paediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) should be screened when there is a suspicion of streptococcal infection (Peterson et al., 2000; Singer et al., 1998; Swedo et al., 1998) and may be important in evaluating the adequacy and response to treatments such as plasma exchange (Nicolson et al., 2000).

It is unclear whether a differential response for hypothetical subtypes of OCD should be considered in the definition of non-response. For example, in patients with severe hoarding symptoms, should dopamine blockers or stimulants be included in a patient's treatment before defining non-response (Black, 1998; Stein et al., 1997)? In reporting response rates, perhaps the response of cases of severe hoarding behaviour, which have a poorer outcome following treatment with SRIs, should be reported separately (Black et al., 1998; Mataix-Cols et al., 1999; Winsberg et al., 1999) from the rates of other non-responsive OCD patients. Perhaps treatment for these patients should avoid 'solo' SSRI treatment and start directly with combination with neuroleptics; only after that treatment could the patient be considered non-responsive to adequate treatment. Adequate treatment utilizing other categories of drugs for specific subtypes should also be evaluated: for example, patients with prevalent symmetry and atypical obsessions or high level of anxiety to treatment may warrant the use of an MAOI (monoamine oxidase inhibitor) (Jenike et al., 1997) or

NSRI (norepinephrine serotonin reuptake inhibitor) (Grossman and Hollander, 1996), and/or augmentation with atypical neuroleptics such as risperidone (McDougle et al., 2000) and olanzapine (Bogetto et al., 2000; Koran et al., 2000) before declaring a patient non-responsive. Highly anxious obsessional subjects could also be treated with a combination of benzodiazepines (i.e. clonazepam) and an SSRI (Hewlett et al., 1990, 1992).

Comorbidity

Another issue in determining non-response to treatment involves the presence of comorbid conditions. While excluding patients with comorbidity from analyses of response to treatment has the advantage of reducing hete26ogeneity, the results also have less generalizability. Non-responsive patients are more likely to meet criteria for comorbid Axis I or Axis II disorders and the presence of a specific comorbid condition could be a distinguishing feature in OCD, with influence on the treatment adequacy and outcome. While coexisting depression is generally irrelevant to treatment response (Katz and DeVeaugh-Geiss, 1990; Mavissakalian et al., 1985), a lower response rate has been observed with comorbid chronic tic disorder (Goodman et al., 1992; McDougle et al., 1993a), and OCD patients with neurological soft signs (Hollander et al., 1990). A comorbid Axis II diagnosis of schizotypal, borderline, and avoidant personality also seems to predict a poorer treatment outcome (Baer et al., 1992), as does obsessive–compulsive personality disorder (Cavedini et al., 1997). While it is still controversial whether comorbid personality disorders change following treatment (Diaferia et al., 1997; Ricciardi et al., 1992), the definition

of adequate treatment for OCD patients with a comorbid Axis II condition, as well as those without such a condition, should include a cognitive and behavioural therapy (CBT) trial before concluding non-response. While recommendations on treatment choice for OCD (both with and without comorbid disorders) and treatment options for non-responders have been addressed by others, including the Expert Consensus Guideline Series (March et al., 1997), the issue being addressed is whether lack of response to the assortment of treatments should define different levels of non-response. While Table 1 is similar to an algorithm for categorizing the effect of the current treatment approach, Table 2 enables individual clinicians to decide the 'next step' approach. For example, if a partial response is experienced with a treatment, then the current treatment should be reinforced; if there is no response or a negative response to the treatment, then a change of treatment is indicated. Additionally, assigning a category of non-response to patients is important for research. Standardizing the categories of patients enables comparison across studies and in meta-analyses.

Adequate treatment: are SRIs the only adequate trials to define non-response?

The positive results of placebo-controlled, double-blind studies have led to the designation of several SRIs by the Food and Drug Administration as the only class of drug with an indication to treat OCD. Serotonin dysfunction has been described as playing a role in the pathophysiology of OCD (Zohar, 1992) and strong support for this hypothesis is demonstrated by the selective efficacy of SRIs. To date, adequate trials are considered to be 12-wk trials of at least moderate doses of SRIs, i.e. clomipramine (150 mg/d), fluoxetine (40 mg/d), sertraline (100 mg/d), paroxetine (40 mg/d), fluvoxamine (200 mg/d), citalopram (40 mg/d) and venlafaxine (225 mg/d). On the basis of this somewhat tautological conceptualization (OCD responds to SSRIs, therefore SSRIs are the treatment of choice for OCD; conditions not responsive to SSRIs are not OCD), and because the definition of subtype and the importance of comorbid conditions in the choice of the treatment are not yet accepted, a large portion of treatment strategies follow the line of the 5-HT hypothesis (Goodman, 1999). These include: enhancing the serotonergic action of the drugs through dosage increase (even if the clinical outcome does not correlate with plasma level of SRIs such as sertraline and fluoxetine), switching and combining SRIs (Figueroa, 1998; March et al., 1997; Pallanti et al., 1999). Another strategy that has been used to enhance serotonergic action is the use of alternative routes of administration of SRIs such as intravenous administration (Fallon et al., 1998; Pallanti and Quercioli, 2000). Intravenous treatment with clomipramine has been reported effective for OCD patients with a history of inadequate response to oral treatment with the same drug (Fallon et al., 1998; Koran et al., 1997), and it is, in a large percentage of cases, the first-line treatment in Italy and other European countries for severe cases. Therefore, the route of administration may have an important impact on resistance to treatment and, as such, intravenous administration should be considered a reasonable treatment choice and used in determining the rate of response of severe cases.

CBT is not only a reasonable first-line therapy, as well as SSRIs, but its application as an augmentation therapy in patients with associated personality disorders (AuBuchon and Malatesta, 1994) or dissociative symptoms (Shusta, 1999) who have been treated with SSRIs but are still symptomatic (Simpson et al., 1999) is particularly indicated. In cases of non-response, CBT must be routinely and consistently integrated with SSRI treatment (Van Noppen et al., 1998), and be used as an augmentation strategy at the various levels of non-response (March et al., 1997) in line with the 5-HT hypothesis (Neziroglu et al., 1990).

Drug strategies have gone beyond the serotonergic hypothesis and started to explore alternative biochemical hypotheses. This is an important approach, especially for OCD patients with subtypes or comorbid conditions. For patients with Axis II sub-threshold or full-blown personality disorders (e.g. schizotypal) neuroleptic augmentation strategies could be indicated. Examples of other possible matching therapies might be:

OCD + tics = SSRI + neuroleptic (typical or atypical) (McDougle et al., 2000),

OCD + anxiety = SSRI + CBT or MAOI (partially supported by Jenike et al., 1997).

Would it not be more reasonable to label a patient a 'non-responder' after a matching therapy has failed?

Use of polypharmacotherapy is becoming common in clinical practice (Laird, 1996) but not in clinical trials. This results in a discrepancy of non-response: monotherapy, for published studies, and polypharmacy for clinical practice. In clinical practice, only polytherapy-treated patients would be included in a sample of non-responders, and not monotherapy-treated patients. However, if that is so, then we must define response for these treatments. According to the Expert Consensus Guideline Series (March et al., 1997), psychiatrists and psychologists recommend starting with CBT or CBT plus an SSRI, depending on the severity and pattern of comorbidity. Experts generally consider CBT a first-line augmentation

strategy and medication augmentation a second-line option. Differences in the chronology of the interventions (if first CBT then SRI or vice versa) should be considered in the definitions of non-response subjects.

Number, type, duration of failed trials

A good response to a tricyclic such as clomipramine in patients with a diagnosis of depression is in 95 % of cases a predictor of a good response to another primarily serotonergic agent such as amitriptyline (Mattes, 1994; Sacchetti et al., 1994). A few studies comparing different SRIs have shown that we cannot consider the SRIs as a homogenous category, such as tricyclics, but as a team with different players; within the category of the so-called SSRIs the percentage of concordance in treating depression is less than 75 % (Sacchetti et al., 1994; Salzman, 1996). Because a first-line SSRI treatment in OCD has not been established, the choice of first treatment is currently based only on the clinician's judgement. However, this choice may have a clear effect on the number of trials adopted, and later, on the designation of a patient as resistant. If an OCD patient does not respond to the first SRI chosen, such as fluoxetine, is that patient a SRI non-responder? Or could the patient have been a full-responder to fluvoxamine as first treatment (Mattes, 1994)? Unfortunately, patients who failed to respond to one or more SRI trials may be less likely than naive patients to respond to further SRI trials (Ackerman et al., 1998). While it is currently unclear whether the sequence of treatment choice truly affects subsequent outcome, motivation to treat with another agent of the same class is typically reduced in exponential progression with each one that fails to elicit a response. Further clarification of the definition of response/non-response, together with subsequent support from clinical trials, should ultimately help to address the question of the number, type, and sequence of treatments for patients with OCD.

With regard to the duration of treatment, especially for preventing relapse, adequate studies have not been conducted. Prolonged trials should be studied, since naturalistic observation suggests that longer treatment prevents relapse and there is evidence that higher doses of prolonged duration (6 months) have turned 50 % of non-responders into responders. Table 1 is a model of suggested stages of response. Through a methodical progression of research based on definitions of non-response, we may ultimately be able to characterize levels of response, as seen in Table 2. This is based on the expert consensus of our group, that parallel those proposed by the group of Michael Thase (Ninan et al., 2001) in respect of the same staging for depression.

Discussion

There are various reasons to create operational criteria for non-response in OCD. Non-response to treatment in OCD is associated with serious social disability: patient suffering, family suffering, and an elevated suicide rate (Hollander et al., 1996). Non-responsive patients are numerous, and their profiles are difficult to cluster due to ambiguities in diagnostic criteria, the possibility of subtypes, and high rates of comorbidity. Moreover, the findings of current studies of 'so-called' non-responsive cases, which guide the evolution of treatment, are currently non-generalizable because of the lack of an operational definition. Furthermore, there is a significant discrepancy in treatment strategies between academic research (with its general acceptance of linear, monotherapeutic strategies, primarily focused on understanding the disease and treatment process and avoiding interference from too many variables) and general psychiatric clinical practice (in which the clinicians try to maximize response by using as many 'variables' as they believe may help), which creates a dichotomy in communication and the direction of research.

These are compelling reasons to clarify the concept of OCD non-response. Our practical objectives, with this paper, are:

(1) To enhance the attention of the clinician to non-responsive cases.
(2) To encourage the use of instruments in clinical practice and research (such as the Y-BOCS) in order to better characterize response/non-response.
(3) To advocate the use of measurements of quality of life and subjective experience of severity and change (e.g. CGI, HRQL) in patient assessment in order to share the therapeutic process with the patient and in order to capture the full clinical picture.
(4) To enable clustering of patients based on reliable and valid conceptual criteria.
(5) To establish a template for non-response 'stages' in OCD, thereby increasing the possibility for communication between researchers and clinicians, both for patient care and research purposes.
(6) To facilitate data collection across multiple sites, crossing both cultural and ethnic boundaries, and explore potential biases that may affect diagnostic or treatment criteria.
(7) To encourage the participation of those with expertise from other backgrounds (such as advocacy associations, psychologists, GPs, etc.) (Sniderman, 1999) in consensus conferences, as diversity in membership is necessary to improve agreement between different points of view on quality-of-life issues.

One of the primary aims is the adoption of the 'staging of response' as an attempt to define chronological milestones to guide drug changes, dose increase, shifts to other SRIs or to another medication class or augmentation agent (Quitkin et al., 1996), and the search for more refined treatment algorithms.

This purpose is not an end, but a starting point towards moving past anecdotal case reports and implementing treatment strategies developed from evidence-based medicine for partial and non-responsive OCD patients.

References

Abramowitz JS, Foa EB (1998). Worries and obsessions in individuals with obsessive–compulsive disorder with and without comorbid generalized anxiety disorder. *Behavior Research and Therapy* 36, 695–700.

Ackerman DL, Greenland S, Bystritsky A (1998). Clinical characteristics of response to fluoxetine treatment of obsessive–compulsive disorder. *Journal of Clinical Psychopharmacology* 18, 185–92.

Angst J, Kupfer DJ, Rosenbaum JF (1996). Recovery from depression: risk or reality? *Acta Psychiatrica Scandinavica* 93, 413–419.

Apter A, Fallon Jr. TJ, King RA, Ratzoni G, Zohar AH, Binder M, Weizman A, Leckman JF, Pauls DL, Kron S, Cohen DJ (1996). Obsessive–compulsive characteristics: from symptoms to syndrome. *Journal of American Academy of Child Adolescent Psychiatry* 35, 907–912.

AuBuchon PG, Malatesta VJ (1994). Obsessive compulsive patients with comorbid personality disorder: associated problems and response to a comprehensive behavior therapy. *Journal of Clinical Psychiatry* 55, 448–453.

Baer L, Jenike MA, Black DW, Treece C, Rosenfeld R, Greist J (1992). Effect of axis II diagnoses on treatment outcome with clomipramine in 55 patients with obsessive–compulsive disorder. *Archives of General Psychiatry* 49, 862–866.

Baron-Cohen S, Wheelwright S (1999). Obsessions in children with autism or Asperger syndrome. Content analysis in terms of core domains of cognition. *British Journal of Psychiatry* 175, 484–490.

Black DW, Monahan P, Gable J, Blum N, Clancy G, Baker P (1998). Hoarding and treatment response in 38 nondepressed subjects with obsessive–compulsive disorder. *Journal of Clinical Psychiatry* 59, 420–425.

Bogetto F, Bellino S, Vaschetto P, Ziero S (2000). Olanzapine augmentation of fluvoxamine-refractory obsessive–compulsive disorder (OCD): a 12-week open trial. *Psychiatry Research* 96, 91–98.

Busatto GF, Buchpiguel CA, Zamingnani DR, Garrido GE, Glabus MF, Rosario-Campos MC, Castro CC, Maia A, Rocha ET, McGuire PK, Miguel EC (2001). Regional cerebral blood flow abnormalities in early-onset obsessive–compulsive disorder: an exploratory SPECT study. *Journal of American Academy of Child Adolescent Psychiatry* 40, 347–354.

Camarena B, Rinetti G, Cruz C, Gomez A, de La Fuente JR, Nicolini H (2001). Additional evidence that genetic variation of MAO-A gene supports a gender subtype in obsessive–compulsive disorder. *American Journal of Medical Genetics* 105, 279–282.

Castle DJ, Groves A (2000). The internal and external boundaries of obsessive–compulsive disorder. *Australian and New Zealand Journal of Psychiatry* 34, 249–255.

Cavedini P, Erzegovesi S, Ronchi P, Bellodi L (1997). Predictive value of obsessive–compulsive personality disorder in antiobsessional pharmacological treatment. *European Neuropsychopharmacology* 7, 45–49.

Chacko RC, Corbin MA, Harper RG (2000). Acquired obsessive–compulsive disorder associated with basal ganglia lesions. *Journal of Neuropsychiatry and Clinical Neurosciences* 12, 269–272.

CMI Group (1991). Clomipramine in the treatment of patients with obsessive–compulsive disorder. The clomipramine collaborative study group. *Archives of General Psychiatry* 48, 730–738.

Diaferia G, Bianchi I, Bianchi ML, Cavedini P, Erzegovesi S, Bellodi L (1997). Relationship between obsessive–compulsive personality disorder and obsessive–compulsive disorder. *Comprehensive Psychiatry* 38, 38–42.

Dominguez RA (1992). Serotonergic antidepressants and their efficacy in obsessive compulsive disorder. *Journal of Clinical Psychiatry* 52, 56–59.

Dominguez RA, Mestre SM (1994). Management of treatment-refractory obsessive compulsive disorder patients. *Journal of Clinical Psychiatry* 55, 86–92.

Emsley RA (1999). Partial response to antipsychotic treatment: the patient with enduring symptoms. *Journal of Clinical Psychiatry* 60 (Suppl. 23), 10–13.

Fallon BA, Liebowitz MR, Campeas R, Schneier FR, Marshall R, Davies S, Goetz D, Klein DF (1998). Intravenous clomipramine for obsessive–compulsive disorder refractory to oral clomipramine: a placebo-controlled study. *Archives of General Psychiatry* 55, 918–924.

Fava GA, Grandi S, Zielezny M, Canestrari R, Morphy MA (1994). Cognitive behavioral treatment of residual symptoms in primary major depressive disorder. *American Journal of Psychiatry* 151, 1295–1299.

Figueroa Y, Rosenberg DR, Birmaher B, Keshavan MS (1998). Combination treatment with clomipramine and selective serotonin reuptake inhibitors for obsessive–compulsive disorder in children and adolescents. *Journal of Clinical Adolescent Psychopharmacology* 8, 61–67.

Frank E, Prien RF, Jarrett RB, Keller MB, Kupfer DJ, Lavori PW, Rush AJ, Weissman MM (1991). Conceptualization

and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Archives of General Psychiatry 48*, 851–855.

Goodman WK (1999). Obsessive compulsive disorder: diagnosis and treatment. *Journal of Clinical Psychiatry 60* (Suppl. 18), 27–32.

Goodman WK, McDougle CJ, Barr LC, Aronson SC, Price LH (1993). Biological approach to treatment-resistant obsessive–compulsive disorder. *Journal of Clinical Psychiatry 54* (6 Suppl.), 16–26.

Goodman WK, McDougle CJ, Price LH (1992). Pharmacotherapy of obsessive–compulsive disorder. *Journal of Clinical Psychiatry 53* (4 Suppl.), 29–37.

Goodman WK, Price LH (1982). Assessment of severity and change in obsessive compulsive disorder. *Psychiatric Clinics of North America 15*, 861–869.

Goodman WK, Price LH, Delgado PL, Palumbo J, Kristal JH, Nagy LM, Rasmussen SA, Heninger GR, Charney DS (1990). Specificity of serotonin reuptake inhibitors in the treatment of obsessive–compulsive disorder. *Archives of General Psychiatry 47*, 577–585.

Grossman R, Hollander E (1996). Treatment of obsessive–compulsive disorder with venlafaxine. *American Journal of Psychiatry 153*, 576–577.

Guyatt GH, Sackett DL, Cook DJ (1993). Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *Journal of the American Medical Association 270*, 2598–2601.

Guyatt GH, Sackett DL, Cook DJ (1994). Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *Journal of the American Medical Association 271*, 59–63.

Guyatt GH, Sinclair J, Cook DJ, Glasziou P (1999). Users' guides to the medical literature: XVI. How to use a treatment recommendation. Evidence-Based Medicine Working Group and the Cochrane Applicability Methods Working Group. *Journal of the American Medical Association 281*, 1836–1843.

Hewlett WA, Vinogradov S, Agras WS (1990). Clonazepam treatment of obsessions and compulsions. *Journal of Clinical Psychiatry 51*, 158–161.

Hewlett WA, Vinogradov S, Agras WS (1992). Clomipramine, clonazepam and clonidine treatment of obsessive–compulsive disorder. *Journal of Clinical Psychopharmacology 12*, 420–430.

Hollander E, Kwon JH, Stein DJ, Broatch J, Rowland CT, Himelein CA (1996). Obsessive–compulsive and spectrum disorders: overview and quality of life issues. *Journal of Clinical Psychiatry 57* (Suppl. 8), 3–6.

Hollander E, Pallanti S (2002). Current and experimental therapeutics of obsessive–compulsive disorder. In: *Psychopharmacology – Fifth Generation of Progress*. (pp. 1647–1664). Lippincott/Williams and Wilkins, New York: Raven Press..

Hollander E, Schiffman E, Cohen B, Rivera-Stein MA, Rosen W, Gorman JM, Fyer AJ, Papp L, Liebowitz MR (1990). Signs of central nervous system dysfunction in obsessive–compulsive disorder. *Archives of General Psychiatry 47*, 27–32.

Jefferson JW, Altemus M, Jenike MA, Pigott TA, Stein DJ, Greist JH (1995). Algorithm for treatment of obsessive–compulsive disorder. *Psychopharmacology Bulletin 31*, 487–490.

Jenike MA, Baer L, Minichiello WE, Rauch SL, Buttolph ML (1997). Placebo-controlled trial of fluoxetine and phenelzine for obsessive–compulsive disorder. *American Journal of Psychiatry 154*, 1261–1264.

Jenike MA, Rauch SL (1994). Managing the patient with treatment-resistant obsessive compulsive disorder: current strategies. *Journal of Clinical Psychiatry 55*, 11–17.

Jenike MA (1992). Pharmacologic treatment of obsessive compulsive disorders. *Psychiatric Clinics of North America 15*, 895–919.

Katz RJ, DeVeaugh-Geiss J (1990). The antiobsessional effects of clomipramine do not require concomitant affective disorder. *Psychiatry Research 31*, 121–129.

Koran LM (2000). Quality of life in obsessive–compulsive disorder. *Psychiatric Clinics of North America 23*, 509–517.

Koran LM, Ringold AL, Elliott MA (2000). Olanzapine augmentation for treatment-resistant obsessive–compulsive disorder. *Journal of Clinical Psychiatry 61*, 514–517.

Koran LM, Sallee FR, Pallanti S (1997). Rapid benefit of intravenous pulse loading of clomipramine in obsessive–compulsive disorder. *American Journal of Psychiatry 154*, 396–401.

Laird LK (1996). Issues in the monopharmacotherapy and polypharmacotherapy of obsessive–compulsive disorder. *Psychopharmacology Bulletin 32*, 569–578.

Leckman JF, Grice DE, Boardman J, Zhang H, Vitale A, Bondi C, Alsobrook J, Peterson BS, Cohen DJ, Rasmussen SA, Goodman WK, McDougle CJ, Pauls DL (1997). Symptoms of obsessive–compulsive disorder. *American Journal of Psychiatry 154*, 911–917.

Leonard HL, Swedo SE, Lenane MC, Rettew DC, Cheslow DL, Hamburger SD, Rapoport JL (1991). A double–blind desipramine substitution during long-term clomipramine treatment in children and adolescents with obsessive–compulsive disorder. *Archives of General Psychiatry 48*, 922–927.

Leonard HL, Swedo SE, Lenane MC, Rettew DC, Hamburger SD, Bartko JJ, Rapoport JL (1993). A 2- to 7-year follow-up study of 54 obsessive–compulsive children and adolescents. *Archives of General Psychiatry 50*, 429–439.

Maina G, Albert U, Bogetto F (2001). Relapses after discontinuation of drug associated with increased resistance to treatment in obsessive–compulsive disorder. *International Clinical Psychopharmacology 16*, 33–38.

March JS, Frances A, Kahn DA, Carpenter D (Eds.) (1997). The Expert Consensus Guideline Series: treatment of obsessive–compulsive disorder. *Journal of Clinical Psychiatry 58* (Suppl. 4), pp. 4–6.

Mataix-Cols D, Rauch SL, Manzo PA, Jenike MA, Baer L (1999). Use of factor-analyzed symptoms dimension to predict outcome with serotonin reuptake inhibitors and placebo in the treatment of obsessive–compulsive disorder. *American Journal of Psychiatry* 156, 1409–1416.

Mattes JA (1994). Fluvoxamine in obsessive–compulsive nonresponders to clomipramine or fluoxetine. *American Journal of Psychiatry* 151, 1524.

Mavissakalian M, Turner SM, Michelson L, Jacob R (1985). Tricyclic antidepressants in obsessive–compulsive disorder: antiobsessional or antidepressant agents? II. *American Journal of Psychiatry* 142, 572–576.

McDougle CJ, Epperson CN, Pelton GH, Wasylink S, Price LH (2000). A double-blind, placebo-controlled study of risperidone addition in serotonin reuptake inhibitor-refractory obsessive–compulsive disorder. *Archives of General Psychiatry* 57, 794–801.

McDougle CJ, Goodman WK, Leckman JF, Barr LC, Heninger GR, Prince LH (1993a). The efficacy of fluvoxamine in obsessive–compulsive disorder: effects of comorbid chronic tic disorder. *Journal of Clinical Psychopharmacology* 13, 354–358.

McDougle CJ, Goodman WK, Leckman JF, Price LH (1993b). The psychopharmacology of obsessive compulsive disorder. Implications for treatment and pathogenesis. *Psychiatric Clinics of North America* 15, 749–766.

Mundo E, Bareggi SR, Pirola R, Bellodi L (1999). Effect of acute intravenous clomipramine and antiobsessional response to proserotonergic drugs: is gender a predictive variable? *Biological Psychiatry* 45, 290–294.

Mundo E, Bareggi SR, Pirola R, Bellodi L, Smeraldi E (1997). Long-term pharmacotherapy of obsessive–compulsive disorder: a double blind controlled study. *Journal of Clinical Psychopharmacology* 17, 4–10.

Neziroglu F, Steele J, Yaryura-Tobias JA, Hitri A, Diamond B (1990). Effect of Behaviour therapy on serotonin level in obsessive–compulsive disorder. *Psychiatry: A World Perspective* 3, 707–710.

Nicolson R, Swedo SE, Lenane M, Bedwell J, Wudarsky M, Gochman P, Hamburger SD, Rapoport JL (2000). An open trial of plasma exchange in childhood-onset obsessive–compulsive disorder without poststreptococcal exacerbations. *Journal of the American Academy of Child and Adolescent Psychiatry* 39, 1313–1315.

Ninan P, Rush J, Altshuler L, Demitrack M, Entsuah R, Gorman J, Rudolph R, Sackeim H, Schooler N, Thase M (2001). Remission and demonstrating efficacy in clinical trials. American College of Neuropsychopharmacology, 40th Annual Meeting, 9–12 December, Waikoloa, Hawaii, Scientific Abstract, p. 93.

Orloff LM, Battle MA, Baer L, Ivanjack L, Pettit AR, Buttolph ML, Jenike MA (1994). Long-term follow-up of 85 patients with obsessive–compulsive disorder. *American Journal of Psychiatry* 151, 441–442.

Pallanti S, Quercioli L, Paiva RS, Koran LM (1999). Citalopram for treatment-resistant obsessive–compulsive disorder. *European Psychiatry* 14, 101–106.

Pallanti S, Quercioli L (2000). Intravenous citalopram in obsessive–compulsive patients non-responders to SRI. *ACNP 39th Annual Meeting Abstract Book*, p. 165.

Pato MT, Hill JL, Murphy DL (1990). A clomipramine dosage reduction study in the course of long-term treament of obsessive–compulsive disorder patients. *Psychopharmacology Bulletin* 26, 211–214.

Pato MT, Zohar-Kadouch R, Zohar J, Murphy DL (1988). Return of symptoms after discontinuation of clomipramine in patients with obsessive–compulsive disorder. *American Journal of Psychiatry* 145, 1521–1525.

Perugi G, Akiskal HS, Gemingnani A, Pfanner C, Presta S, Milanfranchi A, Lensi P, Avagli S, Maremmani I, Cassano GB (1998). Episodic course in obsessive–compulsive disorder. *European Archives of Psychiatry and Clinical Neuroscience* 248, 240–244.

Peterson BS, Leckman JF, Tucker D, Scahill L, Staib L, Zhang H, King R, Cohen DJ, Gore JC, Lombroso P (2000). Preliminary findings of antistreptococcal antibody titers and basal ganglia volumes in tic, obsessive–compulsive, and attention deficit/hyperactivity disorders. *Archives of General Psychiatry* 57, 364–372.

Piccinelli M, Pini S, Bellantuono C, Wilkinson G (1995). Efficacy of drug treatment in obsessive–compulsive disorder. A meta-analytic review. *British Journal of Psychiatry* 166, 424–443.

Pigott TA, Seay SM (1999). A review of the efficacy of selective serotonin reuptake inhibitors in obsessive–compulsive disorder. *Journal of Clinical Psychiatry* 60, 101–106.

Quitkin FM, McGrath PJ, Stewart JW, Ocepek-Welikson K, Taylor BP, Nunes E, Deliyannides D, Agosti V, Donovan SJ, Petkova E, Klein DF (1996). Chronological milestones to guide drug change. When should clinicians switch antidepressants? *Archives of General Psychiatry* 52, 785–792.

Rasmussen SA, Eisen JL (1997). Treatment strategies for chronic and refractory obsessive–compulsive disorder. *Journal of Clinical Psychiatry* 58 (Suppl. 13), 9–13.

Rasmussen SA, Eisen JL, Pato MT (1993). Current issues in the pharmacological management of obsessive–compulsive disorder. *Journal of Clinical Psychiatry* 54, 4–9.

Ravizza L, Maina G, Bogetto F (1997). Episodic and chronic obsessive–compulsive disorder. *Depression and Anxiety* 6, 154–158.

Ricciardi JN, Baer L, Jenike MA, Fischer SC, Sholtz D, Buttolph ML (1992). Changes in DSM-III-R axis II diagnoses following treatment of obsessive–compulsive disorder. *American Journal of Psychiatry* 149, 829–831.

Sacchetti E, Conte G, Guarneri L (1994). Are SSRI antidepressants a clinically homogeneous class of compounds? *Lancet* 344, 126–127.

Salzman C (1996). Heterogeneity of SSRI response. *Harvard Review of Psychiatry* 4, 215–217.

Saxena S, Wang D, Bystritsky A, Baxter Jr. LR (1996). Risperidone augmentation of SRI treatment for refractory obsessive–compulsive disorder. *Journal of Clinical Psychiatry* 57, 303–306.

Scicutella A (2000). Late-life obsessive–compulsive disorder and Huntington's disease. *Journal of Neuropsychiatry and Clinical Neuroscience 12*, 288–289.

Shea MT, Leon AC, Mueller TI, Solomon DA, Warshaw MG, Keller MB (1996). Does major depression result in lasting personality change? *American Journal of Psychiatry 153*, 1404–1410.

Shusta SR (1999). Successful treatment of refractory obsessive–compulsive disorder. *American Journal of Psychotherapy 53*, 377–391.

Simpson H, Gorfinkle K, Liebowitz M (1999). Cognitive-behavioral therapy as an adjunct to serotonin reuptake inhibitors in obsessive–compulsive disorder: an open trial. *Journal of Clinical Psychiatry 60*, 584–590.

Singer HS, Giuliano JD, Hansen BH, Hallett JJ, Laurino JP, Benson M, Kiessling LS (1998). Antibodies against human putamen in children with Tourette syndrome. *Neurology 50*, 1618–1624.

Skoog G, Skoog I (1999). A 40-year follow-up of patients with obsessive–compulsive disorder. *Archives of General Psychiatry 56*, 441–442.

Sniderman AD (1999). Clinical trials, consensus conferences, clinical practice. *Lancet 35*, 4327–4330.

Stahl S (2000). The issue of functional versus symptomatic recovery in depression. *Journal of Clinical Psychiatry 61*, 447–448.

Stein DJ, Bouwer C, Hawkridge S, Emsley RA (1997). Risperidone augmentation of serotonin reuptake inhibitors in obsessive–compulsive and related disorders. *Journal of Clinical Psychiatry 58*, 119–122.

Summerfeldt LJ, Richter MA, Antony MM, Swinson RP (1999). Symptom structure in obsessive–compulsive disorder: a confirmatory factor-analytic study. *Behavioral Research and Therapy 37*, 297–311.

Swedo SE, Leonard HL, Garvey M, Mittleman B, Allen AJ, Perlmutter S, Lougee L, Dow S, Zamkoff J, Dubbert BK (1998). Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. *American Journal of Psychiaty 155*, 264–271.

Thienemann M, Koran LM (1995). Do soft signs predict treatment outcome in obsessive–compulsive disorder? *Journal of Neuropsychiatry and Clinical Neurosciences 7*, 218–222.

Van Noppen BL, Pato MT, Marsland R, Rasmussen SA (1998). A time-limited behavioral group for treatment of obsessive–compulsive disorder. *Journal of Psychotherapy and Practical Research 7*, 272–280.

Weiss AP, Jenike MA (2000). Late-onset obsessive–compulsive disorder: a case series. *Journal of Neuropsychiatry and Clinical Neuroscience 12*, 265–268.

Winsberg ME, Cassic KS, Koran LM (1999). Hoarding in obsessive–compulsive disorder: a report of 20 cases. *Journal of Clinical Psychiatry 60*, 591–597.

Zohar J, Kindler S (1992). Update of the serotonergic hypothesis of obsessive–compulsive disorder. *Clinical Neuropharmacology 15* (Suppl. 1, pt A), 257A–258A.