Treatment goals: response and nonresponse

Jean-Paul Macher, MD; Marc-Antoine Crocq, MD

Psychiatric symptomatology is often subjective, but it can be partly made more objective for the purposes of evaluation. Esquirol was the first modern psychiatrist to stress the need for a scientific approach to treatment evaluation. The kinetics of treatment is complex because different components of the clinical picture improve at a different pace. Assessment of treatment requires prior definition of end point, response, and nonresponse. Response is influenced by several factors, such as placebo effect, diagnostic category and subtypes, and patient heterogeneity. Treatment response may be predicted from clinical and biological parameters. This article lists the main causes of nonresponse, and suggests how to remedy them.

 Dialogues Clin Neurosci. 2004;6:83-91.

Keywords: *treatment response; nonresponse to treatment; diagnosis; psychiatry*

Author affiliations: FORENAP, Institute for Research in Neuroscience and Neuropsychiatry, Rouffach, France

Address for correspondence: Dr Jean-Paul Macher, MD, FORENAP, Institute for Research in Neuroscience and Neuropsychiatry, BP 29, 68250 Rouffach, France
(e-mail: jp.macher@ch-rouffach.fr)

Contrary to somatic medicine, psychiatric symptomatology—with the possible exception of behavioral symptoms and social consequences—is not readily described by objective measures. Rather, psychiatric symptoms are produced by the patient's perception and subjective experience. However, this does not preclude attempts to identify, describe, and correctly quantify this symptomatology. This can be achieved in a straightforward manner through psychometric measures, cognitive and neuropsychological tests, and symptom rating scales. Associated laboratory findings can also provide data that correlate with clinical syndromes: in the last few decades, a range of laboratory measures has become commonly used in psychiatry, from neuroendocrine assays to brain imaging, either functional imaging (electroencephalography [EEG], quantitative EEG, evoked potentials, sleep studies, etc) or structural and functional imaging (magnetic resonance imaging [MRI], single-photon emission computed tomography [SPECT], positron emission tomography [PET], etc).

Psychiatric treatment encompasses a whole array of approaches, from psychotherapy to psychopharmacology, electroconvulsive therapy, and clinical hypnosis. It also includes various types of social intervention. Evaluating treatment response implies that the patient's condition, at baseline and after a fixed duration of treatment, can be assessed in a scientific manner. Pharmacotherapy and cognitive-behavioral therapy (CBT) can easily meet this criterion. Traditionally, psychotherapy, with its emphasis on the individual case, is considered less amenable to evaluation of therapeutic response, although there have been many studies.[1]

In many medical situations, treatment aims at reducing or eliminating symptoms; its efficacy must be assessed with the same clinical and laboratory criteria that were used to characterize the disorder. In psychiatry, the symptoms are often modified or improved, but not suppressed. Another pitfall is that treatment response does not depend only on the presenting disorder; it is also

heavily influenced by the patient's personality and environment. In *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*[2] parlance, prognosis lies as much with Axis II as Axis I. In addition, the kinetics of treatment response are complex. The improvement in objective and subjective parameters may follow different courses. Biological parameters might improve, whereas the patient's subjective experience remains unchanged. As is often the case, the patient's subjective experience might improve later than the apparent remission of the illness, only after the subject recovers unfettered exercise of his or her mental life and imagination. The fact that clinical improvement occurs in consecutive stages should be considered when choosing parameters for assessment of treatment response: (i) biological or brain imaging parameters may be adequate to validate immediate treatment effect; and (ii) the change in the patient's subjective experience may be evidenced later by symptom rating scales or global functioning scales. As mentioned above, personality is a key factor for the quality of long-term treatment response. Additionally, treatment duration will be influenced by the persistence (or not) of triggering factors, the concomitant presence of a physical problem, and the patient's social and emotional environment.

Overall, nonresponse to treatment can be considered if the patient's objective condition and subjective experience do not evolve favorably after a therapeutic trial that was coherent with Axis I and Axis II diagnoses, provided adequate pharmacological doses were used, initial physical disorders were controlled, and detrimental extraneous influences were eliminated.

History

Jean Esquirol (1772-1840), a student of Philippe Pinel, was the first to underline the importance of the statistical assessment of treatment response. He stated his faith in evaluation and statistics in his treatise on clinical psychiatry, *Des maladies mentales, considérées sous les rapports médical, hygiénique, et médicolégal* (1838): "The physician … must give a sincere report of his cases of success and failure. … I love statistics in medicine because I believe that it is useful; therefore, I have been using statistics to help me in my research into mental illness for the last 30 years. Statistics is the best instrument to measure the influence of locality, regimen, and treatment methods."[3] In his statistics on patients admitted to the Charenton hospital near Paris over an 8-year period, he reported that a proportion of 1:3 were cured and discharged; he added that the rate was as high as 1:2.33 if incurable patients were excluded from the analysis.[3]

In his textbook, *Allgemeine Psychopathologie*, Karl Jaspers (1883-1969) had a critical approach to using treatment response as an instrument of knowledge (*therapeutischer Erfolg als Erkenntnismittel*). He warned against the reticence to report treatment failure, particularly in psychotherapy, and against the physician's complacent belief that the patient's condition improved thanks to medical intervention.[4]

Therapeutic expectations change with the times. Today, treatment response is considered mostly in the context of pharmacotherapy, whose appearance in the 1950s considerably broadened our therapeutic armamentarium. Expectations were more modest up to the second half of the 20th century, because therapeutic means were considerably less efficient. The foremost psychotropic agent was chloral, which was synthesized in 1832 and recognized as a useful hypnotic for anxious or depressed patients in 1869 by Matthias E. O. Liebreich (1839-1908), a pharmacologist in Berlin. The less severely ill could be managed with hypnotism, introduced by Franz Anton Mesmer (1734-1815) and developed by Jean-Martin Charcot (1825-1893), or by the "rest cure" introduced in 1875 by the American physician Silas Weir Mitchell (1829-1914) for the treatment of neurasthenia. Asylum was the only option for the severely ill. In the 19th century, it was accepted that some patients were incurable. A pessimistic course was part of the theory of degeneration (Bénédict-Augustin Morel [1809-1873]), which posited that the disease could only worsen from one generation to the next.

Recently, there has been a tendency to apply more stringent criteria to measure response. For instance, until a few years ago, regulatory agencies assessed the efficacy of antipsychotics on the basis of the improvement in psychotic symptoms. Today, cognitive and psychosocial outcome variables are also required.

The parameters of response

Many parameters may influence response and nonresponse. We will attempt to group them under a few headings.

Definition of end point and nonresponse

Treatment response can be evaluated as a continuous measure, as a score on a rating scale, eg, the Hamilton Depression Scale (HAM-D), or as a category, such as improved, in remission, or relapsed. Often, different definitions have been used over time to characterize the outcome of treatments. This inconsistency was a problem in depression, for instance, and operational criteria have been proposed to define change points in the course of the illness.[5] Nierenberg et al proposed that the following categorical outcomes are more clinically relevant than the mere improvement in depression rating scale scores: response (without remission), remission, nonresponse, partial response, relapse, recurrence, recovery, and, more recently, depressive breakthrough.[6]

Response to treatment supposes that the therapeutic targets that have been defined a priori—either symptoms or a syndrome—have been significantly modified by treatment. If rating scales are used, it is generally accepted that a change of less than 50% in the initial score is significant. Changes below that threshold will be considered as cases of nonresponse or insufficient response. Insufficient response or nonresponse does not always reflect the lack of efficacy of the drug treatment that was chosen; it may be caused by other factors, including the patient's constitution, concomitant somatic illness, pharmacogenetics (fast or slow drug metabolism), or environment (food or drug interactions).

Placebo response and other biases

The existence of a placebo response leads to the adoption of strict criteria for genuine response, hence the requirement of a 50% improvement in rating scale scores. Placebo response is linked to the patient's emotional ties with the treatment, the clinician's charisma, or the nursing care in hospital. Placebo response wears off or is less significant when the disorder is protracted, severe, or chronic.

Independently of drug effect, several factors may influence response. The natural course of the disease may lead toward spontaneous cure. For instance, 50% of patients with acute posttraumatic stress disorder (PTSD) will heal spontaneously within the first year of the traumatic event. Also, a physician following up a patient in a study will tend to see him or her as slightly improved with ongoing treatment, even in the absence of objective improvement. This "optimistic bias" might arise from the clinician's sincere care for the patient, and also from the fact that success is easier to tolerate than failure. Because of these biases, it is important to consider double-blind drug trials as the best source of information on treatment response rates.

Diagnosis and response

The main purpose of classification is to identify groups of patients who share similar clinical features, so that suitable treatment can be planned and the likely outcome predicted.[7] As shown in *Table I*,[8-10] response rates vary widely in different disorders. In obsessive-compulsive disorder (OCD), up to 40% of patients are considered to be nonresponders to a specific pharmacological treatment.[11] Treatment is notably arduous and protracted for certain "refractory" disorders. An example is anorexia nervosa, in which response rates should be evaluated taking into account the fact that management is long; etiologies are also heterogeneous, and treatment methods are numerous and varied. Chronic conditions may become notoriously intractable, eg, the negative impact of the duration of untreated psychosis has been proven. Personality disorders may interfere with the treatment of a *DSM-IV* Axis I disorder. For instance, depression is much more difficult to treat in a patient with an obsessive-compulsive personality than in someone with a phobic personality.

Some diagnostic categories are seldom seen in a pure and isolated state, but are usually associated with comorbid conditions, which complicate management and are often difficult to treat. Comorbidity frequently raises the issue of a primary or secondary condition. An example is social phobia, which shows a high lifetime risk of comorbidity with other psychiatric disorders and conditions, eg, other anxiety disorders, major depression, and drug or alcohol abuse. Epidemiological studies have reported comorbidity in 70% to 80% of samples of patients with social phobia.[12] Treatment may fail because it is directed at the secondary problem rather than the underlying social phobia. In all patients with depression, alcohol or drug problems, or panic attacks, the alert clinician should routinely ask about phobic avoidance and fear of scrutiny, in order to identify a possible underlying social phobia.[10]

An important question is whether a specific symptomatic profile or a specific clinical subtype within a diagnostic category may better predict treatment response than a general diagnosis.

Disorder	Drugs	No. of patients/ controls	Scales	Response rates	Reference
Depression	Generally antidepressants	NA	NA	70%-90%	Nierenberg et al,[8] 1991
First-episode patients with schizophrenia	Clozapine (open label)	39 patients NA	CGI	51.3%	Hofer et al,[9] 2003
Multiple-episode patients with schizophrenia	Clozapine (open label)	56 patients NA	CGI	46.4%	Hofer et al,[9] 2003
PTSD	12 weeks of double-blind treatment; sertraline (50-200 mg/day) or placebo	100 patients 108 controls	CAPS-2 total severity score IES CGI-S CGI-I	Intent-to-treat end-point analysis. 60% for sertraline; 38% for placebo	Davidson et al,[10] 2001

Table I. Some examples of the proportion of patients responding adequately to treatment. PTSD, posttraumatic stress disorder; NA, not applicable; CGI, Clinical Global Impression scale; CAPS-2, Clinician-Administered PTSD scale; IES, Impact of Event Scale; CGI-S, Clinical Global Impression—Severity; CGI-I, Clinical Global Impression—Improvement.

Symptom profiles and diagnostic and patient subtypes

Within a single diagnostic entity, subtypes respond differently to treatment. For instance, Fava et al[14] proposed the existence of a subgroup of highly irritable and hostile depressed patients, who report anger attacks and have a psychological profile distinct from that of depressed patients without anger attacks; fluoxetine treatment appeared to reduce anger and hostility in these patients. These results suggest that the subgroup of depressed patients with hostility or anger attacks may have differential neuroendocrine profiles and a selective antidepressant response to fluoxetine. However, another study[15] did not support the hypothesis that angry hostile depressed patients are more likely to respond to selective serotonin reuptake inhibitors (SSRIs) than to other classes of medication (desipramine, a primarily noradrenergic reuptake inhibitor, or venlafaxine, a combined serotonin and norepinephrine reuptake inhibitor).

Heterogeneous patient populations

Patient populations are necessarily heterogeneous in terms of gender (see article by Rubinow and Moore in this issue),[16] age, pharmacogenetics, education, motivation, and insight. Beyond obvious sources of variation, other characteristics explain why, within a diagnostic entity, different patients may be respond differently.[17] In the case of PTSD, American studies have reported that war trauma victims respond less well than civilian victims. This was proved in a controlled study by Van der Kolk et al[18] using fluoxetine or placebo for 5 weeks with 31 veterans and 33 civilians.

Prediction of response

A priori indicators of response to treatment would be useful because it would decrease the need to wait for 4 weeks of antidepressant therapy to conclude whether the patient is a responder or not. OCD patients need to be treated for 6 to 8 weeks before concluding that they are nonresponders. Predictors may be clinical or biological parameters and can be registered at baseline or during the course of treatment.

Clinical parameters

The patient's personal history, such as previous response to a specific drug, can be most informative, although there have been few studies on this problem. A few reports have attempted to evaluate the joint predictive value of a number of clinical characteristics, usually with the help of multivariate statistics. For instance, a study by Denys et al[19] aimed to identify clinical predictors of outcome in OCD, and develop an easily applicable method to predict response to drug treatment. One hundred and fifty patients with primary OCD according to *DSM-IV* criteria were randomly assigned to an SSRI (paroxetine) or a serotonin noradrenaline reuptake inhibitor (venlafaxine) in a 12-week, double-blind, comparison trial. The primary

efficacy parameter was the Yale-Brown obsessive-compulsive scale (Y-BOCS) score, and response to treatment was prospectively defined as a decrease from baseline ≥35%. A stepwise multivariate analysis was used to identify predictors. The absence of previous therapy, moderate baseline obsessive-compulsive symptoms (Y-BOCS score <23), and low Hamilton Depressive Rating Scale scores (6-15) were found to be prognostic determinants of good response to pharmacotherapy. The prognostic ability of the prediction model to discriminate between responders and nonresponders was quantified as the area under the receiver operating characteristic curve (ROC area), which was 0.71 (95% confidence interval 0.63-0.8), demonstrating a reasonable discriminatory power. This study is the first to present a model using prediction to estimate the probability of treatment response to antidepressants in OCD patients. Stip et al[20] studied 25 schizophrenic patients as they switched from a typical to an atypical antipsychotic (risperidone, clozapine, or quetiapine) with a computerized cognitive assessment at baseline and at end point. The symptomatic response criterion was a 20% reduction in Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Syndrome Scale (PANSS). It was shown that changes in semantic fluency and orthographic fluency predicted response.

Biological markers

Measures may be relevant at baseline or during the course of treatment. Plasma levels are an example of a biological measure that predicts response. Other biological predictors are obtained from brain imaging techniques. For instance, Hendler et al found that brain PET measures of untreated OCD patients during specific symptom provocation could predict response to a 6-month course of treatment by sertraline.[21]

The relevance of genetic parameters for pharmacodynamics, pharmacokinetics, and the genetic prediction of treatment response are detailed in this volume by Ackenheil and Weber,[22] Morris-Rosendahl and Fiebich,[23] and Hoehe and Kroslak.[24]

Neuroendrocrine parameters might differentiate clinical subgroups and predict response to treatment. Depressed patients with anger attacks had blunted prolactin response to thyrotropin-releasing hormone (TRH) stimulation compared with those without anger attacks. Treatment with fluoxetine was followed by an overall increase in prolactin response to TRH among the depressed patients with anger attacks.[25] Prolactin response to TRH also tended to predict the degree of response to treatment. A study by Correa et al[26] showed that a blunted growth hormone response to clonidine challenge in depressed patients predicted a better antidepressant response to amitryptiline than fluoxetine. The significance of polysomnographic sleep parameters in depression—in particular REM sleep latency—has been extensively studied.[27] P300 event-related potentials have been shown to be useful for the evaluation of cholinesterase inhibitor (ChEI) treatment in demented patients.[20] Centrally acting ChEIs improve cognitive function in Alzheimer's disease (AD) and other forms of dementia. Evaluation of treatment efficacy in dementia is based mainly on subjective assessment methods such as standardized neuropsychological tests. An additional objective tool for the evaluation of drug response would be most helpful. In a study by Werber et al,[28] 32 patients suffering from dementia of several etiologies were treated with ChEIs (tacrine in 19 patients, donepezil in 5 patients, and rivastigmine in 8 patients). Cognitive response was assessed prior to initiation (baseline) and after 26 weeks, as optimal tolerated doses were achieved and maintained (end point). Evaluation included repeated measurements of Mini-Mental State Examination (MMSE), Alzheimer's disease assessment scale cognitive part (ADAS-cog), and P300 event-related potentials. Results demonstrated improvement of the mean ADAS-cog score by 2.0 points, while the MMSE score remained almost unchanged. Mean P300 latency reduced significantly, though mean amplitudes did not change significantly from baseline to end point. Significant correlations were found between mean ADAS-cog and mean P300 latency at baseline and end point, and between mean MMSE and P300 latency at baseline and end point. These data suggest that P300 is a reliable instrument for assessment of cognitive response to ChEIs in demented patients. *Table II* shows other examples of biological measures at baseline that may predict therapeutic outcome.[21,29-32] However, the proportion of variance contributed by each biological predictor to the clinical outcome is not well established.

Management of nonresponse

Causes of nonresponse

Treatment may fail for a wide variety of reasons, which are more numerous than generally thought. In some cases, treatment is "doomed from the start," because the

Disorder	Measure at baseline	Drug	No. of patients/ controls	Symptomatic response criterion	Biological predictor at baseline	Reference
OCD *(DSM-IV)*	SPECT at baseline in untreated patients	Sertraline, 6 months	26 patients NA	YBOCS decrease ≥30%	Brain perfusion during symptom provocation (dorsal-caudal anterior cingulum and right caudate)	Hendler et al,[21] 2003
Treatment-refractory *DSM-III* major affective disorder	PET	Carbamazepine, nimodipine	32 patients 46 controls	CGI-I much or very much improved	Baseline (left insular and left prefrontal) metabolism	Ketter et al,[29] 1999
Schizophrenic patients refractory or intolerant to treatment with typical antipsychotics	Dopamine receptor D_3 genotype	Clozapine, 6 months	32 patients NA	BPRS decrease ≥50%	Allele Gly-9 and genotype Gly-9/Gly-9 are associated with response	Scharfetter et al,[30] 1999
Unipolar major depressive disorder	EEG sleep responses to placebo (baseline sleep) and a single dose of bupropion SR (150 mg orally)	Open-label treatment with bupropion SR, about 8 weeks	20 patients NA	Depression ratings	Responders showed an increase in REM latency following bupropion challenge; nonresponders showed a decrease	Ott et al,[30] 2002
Depressed elderly patients	MRI	Various antidepressant medications	60 patients NA	MADRS at 12 weeks	Patients with small right and total hippocampal volumes were less likely to achieve remission	Hsieh et al,[32] 2002

Table II. Examples of baseline predictions of therapeutic outcome. YBOCS, Yale-Brown Obsessive-Compulsive Scale; CGI-I: Clinical Global Impression–Improvement Score; BPRS, Brief Psychiatric Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; *DSM, Diagnostic and Statistical Manual of Mental Disorders*; OCD, obsessive-compulsive disorder; SPECT, single-photon emission computed tomography; PET, positron emission tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; NA, not applicable; REM, rapid eye movement; SR, slow release.

patient does not take the medication, or because important factors were not properly considered when treatment was initiated. In other cases, problems may arise from treatment titration or follow-up. Various points should be considered:

- The patient's lack of compliance is a frequent cause: more often than not, the patient does not follow the physician's prescription blindly. The individual may be afraid that a full dose will produce side effects or be worried about dependence. Sometimes, the patient may have misunderstood the original instructions.
- The physician may not have considered contraindications.
- The prescribed dose may be incorrect from the start. If the dose were titrated, the duration of active treatment should only be considered from the time the active dose level was reached. Relapse may have occurred because treatment was discontinued too soon.

- Concomitant drugs (eg, carbamazepine) or dietary habits may affect the metabolism of the psychotropic agent. Other metabolic parameters may prevent the drug from reaching a therapeutic blood level.
- The diagnosis may be incorrect, leading to an inappropriate treatment strategy. The diagnosis should be reviewed and the heterogeneity of the diagnostic category considered. For instance, it is well recognized that anxiety symptoms commonly occur with depressive disorders, and are sometimes the presenting feature. If the anxiety is treated, there is little response, but if the depressive disorder is treated, there may be improvement in anxiety as well as in the depressive symptoms.
- A comorbid mental or physical disorder may prevent symptomatic improvement. Thyroid dysregulation is a well-known cause of treatment resistance in depression. The role of an Axis II mental disorder has already been mentioned.
- The patient may prefer to remain symptomatic because of psychological benefits of the sick role.
- Lack of response may be due to the severity of the clinical picture or the long duration of untreated psychosis.
- The role of genetic variation in the form of hypometabolism or hypermetabolism of a drug may cause treatment failure.[22-24,33]

Action in cases of nonresponse

The action in cases of nonresponse to treatment can be deduced from the causes listed above. Possible solutions include:

- *Assessing whether the diagnosis is correct*, and particularly whether personality factors interfere.
- *Maximizing the response to the same drug* (increasing dose or duration of treatment). Measuring plasma levels (in the case of some antidepressants and antipsychotics, such as haloperidol or clozapine) may help determine if the dosage should be adjusted. Therapeutic drug monitoring for some tricyclic antidepressants and lithium is supported on the basis of clearly defined therapeutic ranges. This is particularly important in individuals whose pharmacokinetic characteristics differ from that of the general population or are changing as the result of aging. Serum or plasma samples should be collected once steady-state drug concentrations are achieved.
- *Checking the patient's metabolic status* (normal metabolizer or hypermetabolizer). Checking for the concomitant administration of other drugs that induce hepatic enzymes is also useful.
- *Changing the drug*. The choice of the new drug should be based on considerations such as side-effect profile and personal and family history of response to previous drug treatment. A common practice is to switch to a drug with different neuropharmacological properties, eg, choosing an inhibitor of serotonin and norepinephrine reuptake, in cases in which treatment with an SSRI failed.
- *Combining drugs within the same class*. This is common in daily clinical practice, even though clinical pharmacologists advocate "clean" treatment strategies, with one drug only. Naturalistic surveys and review of prescription patterns show that most patients with schizophrenia receive more than one antipsychotic. This is inadequate when two molecules have the same profile of pharmacological action.
- *Treatment augmentation*. This strategy involves combining drugs from different classes, eg, the augmentation of antidepressant treatment with lithium or thyroid (T_3) hormones.

The strategies outlined above represent usual choices made by psychiatrists. This was demonstrated by Byrne et al[34] in patients being treated for recurrent major depression who experienced a return of depressive symptoms despite a constant maintenance dose of an antidepressant, a phenomenon known as breakthrough depression. A total of 145 psychiatrists responded to a survey about intervention in hypothetical cases of breakthrough depression in patients taking fluoxetine (20 or 40 mg/day), sertraline (100 mg/day), or nortriptyline (100 mg/day). For all drugs and dosages, the most popular choice was increasing the dosage, followed by augmenting with lithium or another antidepressant, or changing to a different drug.

Conclusion

The question of nonresponse is clearly important and has to be considered within the recent evolution of psychiatric classification and treatment.

First, traditional classifications are being increasingly criticized for failing to define homogeneous patient groups, who might respond in a predictable way to a specific treatment. The fact that psychiatric classification is in a state of flux is exemplified by the ongoing revision process of *DSM*. Research in neuroscience is expected to play a major part in the preparation of *DSM-V*.[35] The

necessity for a classification that could better guide treatment choice is manifest.

Second, psychopharmacology is changing. There is an evolution from drugs directed at symptoms toward drugs directed at syndromes and the pathophysiology of psychiatric disorders. New drugs are being evaluated for their overall efficacy, eg, for their efficacy on syndromes and cognition, rather than on a single symptom. More is required today from treatment methods. Patients and clinicians are no longer satisfied with a mere reduction in symptoms. Etiological treatment is an ideal; in some cases, this ideal might become reality.

The notion of nonresponse is best understood in its historical dimension. Our opinion is still influenced by traditional thought patterns. However, nonresponse is likely to be envisaged quite differently in the near future. A few tasks will remain crucial, such as the definition of criteria for treatment response, and the delineation of factors that exert a negative influence on drug efficacy. The problem of nonresponse exists in all domains of medicine. It is crucial for patients and their families to understand that the physicians did all they could and offered the best available treatments to patients who remained nonresponders. ❑

REFERENCES

1. Smith ML, Glass GV, Miller TI. *The Benefits of Psychotherapy.* Baltimore, Md: Johns Hopkins University Press; 1980.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington, DC: American Psychiatric Association; 1994.
3. Esquirol E. *Des maladies mentales considérées sous les rapports médical, hygiénique et médico-légal. Volume 2*. Paris, France: Baillière; 1838.
4. Jaspers K. *Allgemeine Psychopathologie*. 9th ed. Berlin, France: Springer; 1973:692-693.
5. Frank E, Prien RF, Jarrett RB, et al. Conceptualization and rationale for consensus definitions of terms in major depressive disorder. Remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry*. 1991;48:851-855.
6. Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *J Clin Psychiatry*. 2001;62(suppl 16):5-9.
7. Gelder M, Mayou R, Cowen P. *Shorter Oxford Textbook of Psychiatry*. Oxford, UK: Oxford University Press; 2001:87.
8. Nierenberg AA, Keck PE Jr, Samson J, et al. Methodological considerations for the study of treatment-resistant depression. In: Amsterdam JD, ed. *Advances in Neuropsychiatry and Psychopharmacology. Volume 2. Refractory Depression*. New York, NY: Raven; 1991:1-12.
9. Hofer A, Hummer M, Kemmler G, Kurz M, Kurzthaler I, Fleischhacker WW. The safety of clozapine in the treatment of first- and multiple-episode patients with treatment-resistant schizophrenia. *Int J Neuropsychopharmacol*. 2003;6:201-206.
10. Davidson JR, Rothbaum BO, van der Kolk BA, Sikes CR, Farfel GM. Multicenter, double-blind comparison of sertraline and placebo in the treatment of posttraumatic stress disorder. *Arch Gen Psychiatry*. 2001;58:485-492.
11. Sasson Y, Zohar J. New developments in obsessive-compulsive disorder research: implications for clinical management. *Int Clin Pharmacol*. 1996;11:3-12
12. Schneier FR, Johnson J, Hornig CD, Liebowitz MR, Weissman MM. Social phobia: comorbidity and morbidity in an epidemiological sample. *Arch Gen Psychiatry.* 1992;49:282-288.
13. Montgomery SA. Social phobia: diagnosis, severity and implications for treatment. *Eur Arch Psychiatry Clin Neurosci*. 1999;249(suppl 1):S1-S6.
14. Fava M, Rosenbaum JF, Pava JA, McCarthy MK, Steingard RJ, Bouffides E. Anger attacks in unipolar depression. Part 1. Clinical correlates and response to fluoxetine treatment. *Am J Psychiatry*. 1993;150:1158-1163.
15. Bagby RM, Kennedy SH, Schuller DR, et al. Differential pharmacological treatment response in high angry hostile and low angry hostile depressed patients: a retrospective analysis. *J Affect Disord*. 1997;45:161-166.
16. Rubinow, DR, Moore M. Sex-dependent modulation of treatment response. *Dialogues Clin Neurosci*. 2004;6:39-51.
17. Foa E, Davidson JRT, Frances A. The Expert Consensus Guideline Series. Treatment of posttraumatic stress disorder. *J Clin Psychiatry*. 1999;60(suppl):16.
18. Van der Kolk BA, Dreyfuss D, Michaels M, et al. Fluoxetine in posttraumatic stress disorder. *J Clin Psychiatry*. 1994;55:517-522.
19. Denys D, Burger H, Van Megen H, De Geus F, Westenberg H. A score for predicting response to pharmacotherapy in obsessive-compulsive disorder. *Int Clin Psychopharmacol*. 2003;18:315-322.
20. Stip E, Lussier I, Ngan E, Mendrek A, Liddle P. Discriminant cognitive factors in responder and non-responder patients with schizophrenia. *Eur Psychiatry*. 1999;14:442-450.
21. Hendler T, Goshen E, Zwas ST, Sasson Y, Gal G, Zohar J. Brain reactivity to specific symptom provocation indicates prospective therapeutic outcome in OCD. *Psychiatry Res Neuroimag*. 2003;124:87-103.
22. Ackenheil M, Weber K. Differing response to antipsychotic therapy in schizophrenia: pharmacogenomic aspects. *Dialogues Clin Neurosci*. 2004;6:71-77.
23. Morris-Rosendahl, DJ, Fiebich BL. The future of genetic testing for drug response. *Dialogues Clin Neurosci*. 2004;6:27-37.
24. Hoehe MR, Kroslak T. Genetic variation and pharmacogenomics: concepts, facts, and challenges. *Dialogues Clin Neurosci*. 2004;6:5-25.
25. Rosenbaum JF, Fava M, Pava JA, McCarthy MK, Steingard RJ, Bouffides E. Anger attacks in unipolar depression. Part 2. Neuroendocrine correlates and changes following fluoxetine treatment. *Am J Psychiatry*. 1993;150:1164-1168.
26. Correa H, Duval F, Claude MM, et al. Noradrenergic dysfunction and antidepressant treatment response. *Eur Neuropsychopharmacol*. 2001;11:163-168.
27. Riemann D, Berger M, Voderholzer U. Sleep and depression—results from psychobiological studies: an overview. *Biol Psychol*. 2001;57:67-103.
28. Werber EA, Gandelman-Marton R, Klein C, Rabey JM. The clinical use of P300 event-related potentials for the evaluation of cholinesterase inhibitor treatment in demented patients. *J Neural Transm*. 2003;110:659-669.
29. Ketter TA, Kimbrell TA, George MS, et al. Baseline cerebral hypermetabolism associated with carbamazepine response, and hypometabolism with nimodipine response in mood disorders. *Biol Psychiatry*. 1999;46:1364-1374.
30. Scharfetter J, Chaudhry HR, Hornik K, et al. Dopamine D_3 receptor gene polymorphism and response to clozapine in schizophrenic Pakistani patients. *Eur Neuropsychopharmacol*. 1999;10:17-20.
31. Ott GE, Rao U, Nuccio I, Lin KM, Poland RE. Effect of bupropion SR on REM sleep: relationship to antidepressant response. *Psychopharmacology*. 2002;165:29-36.
32. Hsieh MH, McQuoid DR, Levy RM, Payne ME, MacFall JR, Steffens DC. Hippocampal volume and antidepressant response in geriatric depression. *Int J Geriatr Psychiatry*. 2002;17:519-525.
33. Lebrun LH, Villeneuve JP. Hypermetabolism of phenytoin as a cause of treatment failure. *Clin Neuropharmacol*. 1983;6:67-70.
34. Byrne S, Rothschild AJ. Psychiatrists' responses to failure of maintenance therapy with antidepressants. *Psychiatr Serv*. 1997;48:835-837.
35. Kupfer DJ, First MB, Regier DA, eds. *A Research Agenda for DSM-V*. Washington, DC: American Psychiatric Association; 2002.

Objetivos del tratamiento: respuesta y falta de respuesta

La sintomatología psiquiátrica a menudo es subjetiva, pero para los propósitos de una evaluación puede ser, en parte, objetivada. Esquirol fue el primer psiquiatra moderno en dar énfasis a la necesidad de una aproximación científica para la evaluación de un tratamiento. La dinámica del tratamiento es compleja ya que los diferentes componentes del cuadro clínico mejoran a un ritmo diferente. La evaluación de un tratamiento requiere de la definición previa del objetivo final, de la respuesta y de la falta de respuesta. La respuesta está influenciada por diversos factores como el efecto placebo, las categorías diagnósticas y los subtipos, y la heterogeneidad de los pacientes. La respuesta terapéutica se puede predecir mediante parámetros clínicos y biológicos. Este artículo revisa las principales causas de falta de respuesta terapéutica y sugiere cómo remediarlas.

Objectifs du traitement : réponse et non-réponse

La symptomatologie psychiatrique est souvent subjective, mais on peut la rendre en partie plus objective pour les besoins de l'évaluation. Esquirol a été le premier psychiatre moderne à souligner la nécessité d'une approche scientifique pour l'évaluation du traitement. La cinétique du traitement est complexe parce que les différentes composantes du tableau clinique s'améliorent à un rythme différent. L'évaluation du traitement nécessite une définition préalable des critères d'évaluation, de la réponse et de la non-réponse. Plusieurs facteurs influent sur la réponse, tels les effets du placebo, les catégories et sous-types de diagnostics et l'hétérogénéité des patients. La réponse au traitement peut être prévue à partir des paramètres cliniques et biologiques. Cet article passe en revue les principales causes de non-réponse et propose d'y remédier.