

## Who are Resistant Patients? Quality of Treatment and Disease Control

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### Abstract

#### Background:

The correspondence between scientific knowledge and health care practices is essential to grant drug addicts with qualitative improvement in therapeutic units available. The lack of knowledge into effective treatment strategies and poor skills in handling effective instruments may lead to dropping out of apparently resistant patients, whose disease has never been challenged with any potentially effective program.

#### Methods:

We analyzed clinical characteristics and outcomes of standard treatment nonresponder heroin addicts enrolled in the upper-level Pisa University program in 2 subsequent periods, 1993 to 1998 and 1998 to 2004, after their latest relapse.

#### Results:

Period II patients got treatment earlier in their addiction history, but seemed to spend longer time in treatment (successfully or not) before their latest relapse. With regard to outcomes over the years, there has been no decrease in the rate of therapeutic successes and the duration of successfully accomplished treatments. No difference was found either for the duration of treatments with negative outcomes. A worthwhile percentage of patients shows a positive outcome (treatment successfully completed or in progress with success). The maximum administered dosage did not differ with respect to outcome in either period.

#### Conclusions:

Although diagnosis and intervention tend to place first in the history of addicts, effective means of treatment are not systematically resorted to, so that symptomatic patients tend to stay for longer periods and miss stabilization. Treatment units seem to stick to their own habits, so that stabilized patients are offered the same treatments they had shown resistance to.

**Key Words:** drug addiction, effective treatments, quality of assistance, refractoriness

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### THE DRIFT OF THE QUALITY

The quality evaluation in the health field can be accomplished either from a health care-oriented or from a scientific viewpoint. In the first case, we will con-

sider whether health services are accessible, useful, organized, and actionable according to the principles of economy and favorable to the citizen. On the scientific front, we shall establish whether programs are conceived and run in accordance with the standards of effectiveness and specificity, and the system tending to adapt to scientific knowledge to obtain therapeutic results for each category of patients. Although these 2 aspects are relevant to the same object, it must be said that some categories of patients, such as the mentally ill ones or drug addicts, although able to express satisfaction about the assistance they receive, may still ignore if the treatments received actually correspond to those potentially effective. Within a trust-based relationship, the scientific quality is often taken for granted by the patient, which is why it is the physicians who have to be the bearer of this issue to the attention of public institutions. The doctor, in the final analysis, is the only one who can truly distinguish between what is not feasible by the available tools and what is just not realized because of the misuse of available tools.<sup>1</sup> As described by Strain,<sup>2</sup> the quality of health care depends on 3 key factors: the ability to identify ill patients (diagnosis), the availability of treatments granting a positive response for the highest number of users as possible, and finally ensuring that these treatments are accessible so that patients can apply to any center of to obtain the most effective and specific treatments to their case, or continuing any treatment that has already proven effective.

As far as doctors themselves are not directly responsible for the quality of the intervention, intended as expected effectiveness and addressing of

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resources, the achievement of satisfactory levels of care can run up against obstacles of different matrix. For example, the viability of treatments in 1 geographic area may depend arbitrarily on their popularity or on the raising expectations from new treatments, or because the local health manager strongly “believes” in 1 treatment mode, or because he is fond of some kind of treatment because of research competence of perspectives, rather than for health care considerations. Because of this lack of homogeneity, the patient may find the gold-standard treatment with no effort in 1 territory, but may never find anything similar in the area nearby.<sup>3,4</sup>

In contrast, especially in the Anglo-Saxon countries, it is widely thought that the patient should be granted access with equal facility to all existing treatments. This view fails to match the right for assistance from the scientific ground: the patient may choose to undergo less reliable and effective interventions with no barrier with respect to a preference for the gold-standard ones. In this drift, the most effective treatments, often less popular, tend to be deserted in favor of others, as they avoid the perspective of being dependent on a treatment and avoid to embrace the realistic idea of suffering from a chronic disease. The economic solution in some cases results in automatic quality control: a waste of resources is discouraged, as long as it is not offset by a proportional gain in productive and social terms because of the limited funding and the rule to reach out as many clients as possible by the cheapest treatment.<sup>5-7</sup>

The issue of quality is also an important aspect to highlight and resolve some paradoxical nodes in the treatment of addictions. For example, services that practice shorter-term interventions discriminate between success or failure with respect to the accomplishment of the intervention and not with respect to the disease onto which the method was applied. This means assessing the successfulness of a certain intervention based on the ability to perform it correctly, instead of focusing on the impact of that intervention to control the chronic-relapsing course of the disease. In a chronic disease such as drug addiction, the success of short-term actions intended as their fea-

sibility is out of question, but simply not relevant to the objective of changing the course of addiction.<sup>8,9</sup> In addition, the classification of interventions often refers to generic categories and not to a precise protocol: medical versus nonmedical, pharmacological versus nonpharmacological; or to failing conceptual categories, such as maintenance-oriented replacement versus abstinence-oriented antagonism, or drug-free regimens. This approach leads to merged interventions that use the same tools (eg, methadone) with one another, irrespective of the characteristics critical to the success of the program, such as “dose” and “duration,” which are the actual therapeutic tools.<sup>10-15</sup>

Conversely, a program may be labeled as ineffective, although in the absence of the premises for its effectiveness (eg, methadone and/or buprenorphine doses). The risk is that a superficial classification of programs by rough criteria (the use of a certain drug), with no other prerogatives, leads to a low-quality standard, poor individual results, and the transferring of patients to other programs as nonresponders, hardcore, or (what is most absurd) chronically ill. Instead, such subjects may form a population of potential responders and are likely to be nonresponders to treatments with unreasonable limits to dose and duration, let alone the use of wholly ineffective instruments. These limits are totally unfounded with respect to the nature of the disease and the knowledge of therapeutic dynamics,<sup>8,16-18</sup> so that the resulting treatment should be rather classified as “improper” than grouped with others using the same instrument (eg, methadone and/or buprenorphine by the correct technique).

A paradox has been described by which gold-standard treatments seem not to have “given good results” across entire areas and were then abandoned or never spread, so that users can either enroll in ineffective treatment or failing versions of nominally effective.<sup>19,20</sup> The former kind of clients will improve temporarily, but will not be protected against relapse, whereas the latter will be considered hardcore, incurable cases. Eventually, the former will tend to worsen through relapses and join the latter in the long term.

The ideal frontline of the quality of care, that is, the patient-treatment matching,<sup>2</sup> or the building of integrated treatments, or the personalization of care, does not loom in the European horizon. In fact, these concepts are born out of a standard of care, the so-called gold-standard, which is not overwhelmed by the personalization of care, but is a prerequisite to it and must underlie it. To customize and integrate should mean offering something more but not different. A typical example of this unfair practice is to that of a variety of either psychopharmacological or psychosocial interventions, designed as enhancement interventions, but functioning as channels for the disengagement of the patient from the basic treatments.<sup>21</sup> Individuals with a dual diagnosis, for example, may be excluded from the respective therapies because of either diagnoses: some receive psychiatric drugs to control the addiction, and sometimes are shifted toward non-specific psychotropic treatment, which is also proposed as a way to taper-off opiate agonists, or to avoid dose increasing of opiate agonists. This paradox looms as a dead end in terms of quality: patients with a “double trouble” may refer to dedicated centers where anticraving treatments are inadequate as a standard treatment, or apply to psychiatric treatments that are inadequate themselves to control the course of addiction. This shift from the core of the antiaddictive treatments to ancillary or additional options goes along with the attribution of the “therapeutic” label to any available treatment, rather than only to those who target the core addictive symptoms in an effective and reliable way. In contrast, ancillary and additional interventions fail to influence the rate of compliance, retention, and therapeutic alliance in the context of the “core” ongoing agonist treatment program.<sup>6,11,22–24</sup>

### THE POINT OF VIEW OF A SECOND-LEVEL OUTPATIENT CLINIC

A second-level outpatient clinic is a peculiar observation point from within the context of addiction treatment, which may register trends toward pitfalls and

abnormalities in therapeutic histories of subjects who apply to have “a second opinion.” On one side, it is possible to register the rates and features of failed therapeutic attempts; on the other hand, evaluated subjects may be started on viable treatments and eventually read-dressed to their first-line services to be followed up after stabilization. As long as the first-level services granted patients with gold-standard treatments for the majority of patients, applicators to a second-level service should be those who are actually resistant to treatments, although tried at averagely effective dosages and for a reasonable time. In this view, subjects who are started onto special programs for resistant patients may respond because of more complex treatment modalities, that is, multimodal, intensive, or enhanced treatments, or by experimental techniques. Such patients may be later transferred to first-level services once their stabilization regimen has been established. The Dual Diagnosis Unit at Pisa University ran an outpatient methadone maintenance treatment program conceived as a second-level approach with direct administration of therapeutic drugs. The aim was to study and apply treatments for “difficult” patient categories, such as resistant addicts or dual-diagnosed ones, usually addressed to the service after discharge from the nearby psychiatric ward or day-hospital facility. This facility, incorporated in the Neuroscience Department (Section of Psychiatry), would partner first-level local addiction treatment units as a second-level center for addictive diseases, with special regard to methadone (since 1993) and buprenorphine (since 2000). The protocol was designed as a high-threshold one, centered upon pharmacological treatment and pursuing rehabilitation by a path physiological treatment of addiction. After induction into agonist treatment, the dosage is gradually increased until urinalysis turns stably negative for morphine metabolites and benzodiazepines (when not prescribed) for 2 consecutive months. Patients who have achieved such a condition are labeled as “stabilized” or “responder”; however, at any time, the dosage or program settings may be revised or changed so as to recover stabilization in case it is not maintained. No limitations to dose

and duration of treatment are predefined; nevertheless, patients who do not achieve stabilization by the first year are considered as nonresponders and terminated. Those patients are sent (back) to other services to be able to benefit from low-threshold approaches. In the case of buprenorphine, 32 mg is considered the maximum possible stabilization dosage, and nonresponders to ceiling-dose buprenorphine are proposed to enter methadone maintenance straight forward.

The aim of this study was to ascertain whether treatment applicers at Pisa University's second-level outpatient clinic were actually definable as treatment-resistant at the treatment entrance and whether their features underwent any change across the 1993 to 2004 period. Results might be interpreted as indicators of the first-level treatment standards and unmet needs, and their evolution through time. To measure such an evolution, we divided patients into 2 consecutive groups, according to the time of treatment entrance.

## METHODS

### Sample

A total of 219 patients were included in the study, corresponding to those enrolled in a methadone maintenance program across 125 months of activity at the Dual Diagnosis Unit of Pisa University (1999 to 2004). The sample included 153 (69.9%) men and 56 (30.1%) women averagely aged  $30.52 \pm 6.5$  (16 min; maximum, 47). All patients had a diagnosis of heroin according to the various Diagnostic and Statistical Manual of Mental Disorders, eventually confirmed by Diagnostic and Statistical Manual of Mental Disorders IV TR criteria,<sup>25</sup> retrospectively. As many as 64 subjects, who were responders, were still on treatment at the time of study termination. At the time of enrollment, all subjects had given their informed consent to treatment and for the anonymous use of clinical data for research purposes.

The sample, on the basis of the chronology of enrollments along the entire course of the activity, has been divided into 2 subsamples: 1 composed

of 119 subjects, 90 (75.9%) men and 29 (24.1%) women of mean age  $29.57 \pm 5.6$  (minimum, 19; maximum, 46), recruited across 63 months (1993 to 1998; period I); and 1 composed of 100 subjects, 63 (63.0%) men and 37 (37.0%) women with mean age  $31.64 \pm 7.5$  (minimum, 16; maximum, 47), recruited across 62 months (1999 to 2004; period II).

### Survey Instruments

The Drug Addiction History-Questionnaire<sup>26</sup> is a multidimensional questionnaire that comprises the following 8 areas: 1—demographic data, 2—physical health, 3—mental status, 4—social adjustment and environmental factors, 5—substances abused, 6—substance abuse modalities (heroin intake, modality of use, stages of illness, nosography), 7—treatment history, and 8—addiction history (age at first contact, age at onset of continuous use, dependence length, and age at first treatment). The Scale rates 10 presence-absence items: 1—somatic comorbidities, 2—abnormal mental status, 3—work problems, 4—household problems, 5—sexual problems, 6—socialization and leisure time problems, 7—drug-related legal problems, 8—polysubstance abuse, 9—previous treatment, and 10—combined treatments. We encoded the modality of use as follows: 1—stables, 2—junkies, 3—two worlders, and 4—loners, according to Lahmeyer's classification.<sup>27</sup> "Stables" are opioid addicts who espouse conventional values, hold legitimate jobs, are generally law abiding, and do not associate with other addicts. "Hustlers," otherwise called "junkies" or "criminal addicts," are closely identified with an addict subculture, are not legitimately employed, and subsist on the proceeds of criminal activities. "Two-worlder" addicts engage in criminal activities and associate with other addicts, but are also legitimately employed. "Loner" addicts are not involved either in the addict subculture or the conventional culture. They are usually unemployed and live on welfare benefits, rather than on the proceedings of criminal activities. These uninvolved addicts may have severe psychological disorders.

The development of addiction may be considered to consist of 3 stages: 1—acute (immediate) drug effects (Honeymoon stage); 2—transition from recreational use to patterns of use consistent with addiction (Increasing Dose stage); and 3—end-stage addiction, which is characterized by an overwhelming desire to obtain the drug, a diminished ability to control drug seeking and reduced pleasure from biological rewards (Revolving Door stage).<sup>28</sup> Considering the clinical typology, drug addicts can be divided into: 1—reactive (presence of psychosocial stressors before using heroin), 2—self-therapeutic (presence of psychiatric stressors before using heroin), and 3—metabolic (no psychosocial or psychiatric antecedents).<sup>29</sup> We also considered the pattern of use. The user of illicit opioids typically undergoes periods of voluntary or forced abstinence lasting weeks to months followed by period of relapse.

### Statistical Analysis

The 2 period groups were compared for sociodemographic, DAH-RS factors and concomitant substance abuse by means of  $\chi^2$  test for categorical variables and *t* test for continuous ones. All analyses were carried out using the statistical pack-

age of SPSS (version 4.0). As this is an exploratory study, statistical tests were considered significant at the  $P < 0.05$  level.

## RESULTS

### Changes Over Time in the Clinical Characteristics of Subjects Have Been Referred or Have Been Applied for Treatment

Period II enrolled patients differ from peers recruited during period I by the following characteristics (Table 1). A greater number of patients are older than 30 years and have a higher degree of education. Fewer display a pattern of daily use of heroin, fewer are psychosocially impaired or have legal problems. In addition, fewer have a history of methadone maintenance. The large majority of subjects (174, 79.5%) reports at least 1 past therapeutic attempt, and one third has failed in  $>3$  attempts. There are differences in the types of interventions provided: psychotherapy is ongoing for a minority of subjects enrolled in period II, whereas it is not represented at all in period I (4.1% vs. 0.0%,  $P < 0.001$ ). Methadone maintenance is by far the most frequent past attempt for the whole sample (128,

**TABLE 1.** Change of Baseline Variables Between Time Cohorts of Treatment Appliers at a Second Service Level (Resistant Patients) for Addictive Diseases

	1993-1998 Period N = 119	1999-2004 Period N = 100	$\chi^2/t$ Test	P
Age (>30 y old) [n (%)]	49 (41.2)	60 (60.0)	7.70	0.006
Educational level ( $\geq 8$ y) [n (%)]	36 (30.3)	51 (51.0)	9.76	0.001
Frequency of heroin use (at least daily) [n (%)]	97 (83.6)	52 (54.2)	21.81	<0.001
Stable psychosocial pattern* [n (%)]	40 (33.6)	63 (63.0)	18.83	<0.001
Legal problems [n (%)]	61 (51.3)	28 (28.0)	12.18	<0.001
Time between the age of addiction onset and age of first treatment (y)	6 $\pm$ 6	2 $\pm$ 3	5.04	<0.001
Time since first treatment (y)	3 $\pm$ 4	6 $\pm$ 6	-5.14	<0.001
Lifetime methadone maintenance [n (%)]	55 (46.2)	27 (27.0)	8.56	0.003

\*Psychosocial subtype of addicts who have not lost their productive abilities and social contacts, although some grade of deterioration and impairment has taken place with regard to their premorbid functional level. It is to be intended as a category and corresponds to a mild to moderate severity level of addictive symptoms, which currently allows some room for social life and individual functioning in productive areas. In addition, it may be the result of partial response to treatments, or of partially effective treatments.

58.4%), but is more likely to be ongoing or has been terminated in the past among patients enrolled in period I (73.9% vs. 40%,  $P < 0.001$ ).

Period II patients have been addicted for a shorter time until their first treatment attempt, but apply to treatment after a longer period of time since their first treatment attempt. In other words, period II patients get treatment earlier in their addiction history, but seem to spend longer time in treatment (successfully or not) before their latest relapse.

### Features and Outcome of Index Treatment

The parameters and outcome of methadone treatment is shown in Table 2. Over the years, there appears to be no decrease in the rate of therapeutic successes and the duration of successfully accomplished treatments. No difference was found either for the duration of treatments with negative outcomes between the 2 enrollment periods. A worthwhile percentage of patients shows a positive outcome (treatment successfully completed or in progress with success), even accounting for the possibility that some responders may possibly worsen along a further observation period. The duration of treatment is similar for the 2 groups and the stabilization dosage of methadone. The maximum administered dosage did not differ with respect to outcome in either period.

### DISCUSSION

The profile of heroin addicts enrolled in recent years can correspond to that of heroin addicts who are less severely ill (lower level of psychosocial impairment, nonintensive use of heroin) or heroin addicts undergoing a phase of attenuated disease because of the intervention of different factors, for example, under medication with partial effectiveness on certain aspects (level of use, withdrawal symptoms/intoxication).<sup>30</sup>

In the first case, we would expect to dwell with younger heroin addicts, with a shorter disease history and therapeutic curriculum, or heroin addicts who started using heroin late, and therefore have been ill and gone through treatment attempts for a shorter time. However, this assumption is not supported by the present data: in fact, period II heroin addicts are neither young nor have they started using heroin later than usual (early adolescence or adulthood). The age of first use and age of regular use are similar, whereas period II patients enter treatment earlier in the course of their disease, probably reflecting a trend toward early intervention developed by the health care system over the years. Patients are then diagnosed promptly and addressed to some treatment at once, before they reach a higher level of social impairment or develop somatic or legal complications, with the right intent to implement secondary prevention.

**TABLE 2.** Change of Outcome Variables Between Time Cohorts of Treatment Appliers at a Second Service Level (Resistant Patients) for Addictive Diseases

	1993-1998 Period N = 119	1999-2004 Period N = 100	$\chi^2/t$ Test	P
Positive outcome* [n (%)]	68 (57.2)	75 (75.0)	7.64	0.006
Duration of of completed programs (mo)	75 ± 43	58 ± 31	1.13	NS
Duration of of failed programs	30 ± 29	14 ± 20	2.51	0.014
Maximum prescribed dosage	138 ± 75	130 ± 87	0.65	0.513

\*Positive outcome. Progressive extinction of addictive behaviors accompanied by negativization of urinalyses for morphine metabolites in at least 75% of collected samples (refusal of delivering a urine sample is registered as equivalent to a positive result) and Diagnostic and Statistical Manual of Mental Disorders/GAF of at least 60 compliances with program rules (attendance, sample delivery for exams, sticking to prescribed dosages). Negative outcome: noncompliance, failure to achieve stabilization by 1 year.

In contrast, these are the same subjects who would later apply to a second-level service as apparent nonresponders, and after a longer time spent in and out of treatment attempts: in conclusion, the therapeutic course displays some theoretically favorable features (time spent in treatment, latency of first treatment), but still turn out to be unsuccessful. Period II patients are older heroin addicts (more often over 30 y of age) who have spent a longer time as addicts, never reaching satisfactory stabilization.

Were period II patients less likely to be stabilized by treatment because of a higher level of disease severity, we would expect them to have a worse outcome than period I peers. Assuming that the quality and outreach of administered treatment may have improved from period I to II, the retention and response rates may be similar or even higher. Nevertheless, the program's stereotypical characteristics have not changed through the years, and patients do not differ as for disease severity. Retention rates are comparable, although there is room to hypothesize a possible longer-term dropout for period II patients, who are evaluable through a shorter observation period.

Two trends can be described across the 1993 to 2004 period: addicts are diagnosed and referred to treatment earlier; however, their therapeutic attempts do not produce stable remission because of a lower rate of agonist treatment and ineffective variants of the same. Thereby, patients tend to hang around in the middle ground of relapse and short-term nonspecific treatment programs, displaying as apparently resistant or "hard core."<sup>3,4,19,21</sup> A favorable premise to disease control, such as early intervention, is thereby wasted through the omission of effective and specific intervention, aiming at controlling the course of addiction and sustaining the achievement and maintenance of long-term rehabilitative goals.<sup>1,20,31</sup> In fact, only 23 (23%) responders were on methadone treatment at entrance, at an average dose of  $52.61 \pm 44.0$  mg/d (range, 20 to 240 mg/d). Only 9 (9.0%) responders had been prescribed at least 60 mg/d (range, 60 to 70 mg/d), none was taking blocking dosages between 80 and 120 mg/d,<sup>32</sup> and 1 (1.0%) was

taking 240 mg/d. Of the 100 subjects enrolled between 2000 and 2004, approximately half were not in treatment, 39% attended a local addiction treatment unit, and the rest were receiving assistance from specialists or general practitioners, who had not prescribed or referred them to any specific treatment for opiate addiction. As many as 60% of subjects applied on their own (25% following a friend's or relative's advice), 12% had been referred by the nearby psychiatric service after discharge from the ward. A certain number (21%) had been referred to our service by other psychiatrists, a few had been addressed by nonpsychiatrists or addiction treatment staff. None had been oriented by their general practitioner. The presumed nonresponder, then, is not handled by the health care system as a rule, to have him enrolled in a second-level program, as long as the majority of appliers had not been referred by first-level staff. The "word of mouth" seems to be the prevalent source of referral to the second-level program.

In fact, the trend indicated by our data seemed to be later confirmed by official data gathered by first-level services all across the Italian territory, year by year. In the 2011 update of such data, the average treatment program coupled a dose below the minimum recommended level of 60 mg/d and was accomplished within 1 year, usually with satisfactory results (ie, stabilization). Agonist treatments are not used as first-line for the average patient, despite the high rate of treatment response (negative urinalyses) while on treatment: in particular, younger patients (below 30 y of age) are approached by nonagonist treatments. In other words, despite the trend toward earlier treatment, patients tend to undergo ineffective treatment, because of omission of specific interventions, premature termination, or ineffective dosing, so that they get older without obtaining stable remission. This health care situation, intermediate between the low availability of agonist treatment and their adoption as standard first-line interventions at effective dosages and in a long-term perspective, does not produce intermediately satisfactory results, because potential prevention through early

treatment is not coupled to and pathophysiological treatment of addiction and relapse prevention through maintenance of results.

A recent study has been conducted about the adequacy of methadone dosage in addiction treatment units. At present, preliminary data on 492 patients are available in the Italian publishing circuit. Patients were assessed along the Opiate Dosage Adequacy Scale to verify whether administered dosages were consistent with features of clinical effectiveness. Results show that dosages <40 mg are clinically inadequate for 18.3% of the 147 patients, dosages ranging between 40 and 80 mg/d are inadequate for 24% of the 225 patients, and dosages over 80 mg/d are inadequate for 31.8% of the 120 patients. Less than 5% of patients are treated with dosages over 160 mg/d. These data may mean that, although some lower-to-average patients need treatment adjustment by dose increasing, 1 of the 3 patients treated with average to higher dosages need further increase to obtain satisfactory results. As long as a trend toward dose limitation or treatment negotiation at lower dosages exists, potential responders to increased dosages are likely to figure as "resistant" in a failing iatrogenic perspective.

## CONCLUSIONS

Almost in the Italian health care system, but we are supposing in all European countries,<sup>33-38</sup> younger addicts may count on earlier diagnosis and treatment occasions, although effective interventions are far from being proposed as first-line choices, or, when featured, tend to be performers at ineffective dosages or for limited periods of time. Such a mismatch is the source of apparent resistance to treatment, which is not confirmed after the enrollment in a second-level service conceived for resistant patients. In fact, this population shows a high rate of response to agonist maintenance, when performed at average effective dosages, and with no dose limitation, and in a maintenance perspective with no preplanned or arbitrary taper-off phase.

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