A stepwise drug treatment algorithm to obtain complete remission in depression: a Geneva study

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Summary

Questions under study/principles: We describe the proportion of severely depressed outpatients reaching complete remission at the different stages of a drug treatment algorithm. We compare several treatment options for SSRI (selective serotonin reuptake inhibitor) non-responders and test the feasibility of the algorithm in clinical conditions.

Methods: Patients with severe depressive disorders (ICD-10; MADRS ≥25) admitted to an academic outpatient clinic were enrolled in this algorithm-guided sequential treatment protocol (starting with an SSRI and ending with a tricyclic, lithium, triodothyronine combination). The general principle of the algorithm was to boost the drug therapy in the event of non-response.

Results: 135 patients entered the study and 131 were eligible for analysis. From this group, 86 patients dropped out (65.6%), 40 reached complete remission (30.5%) and 5 patients did not reach remission at all (3.8%). In the 117 patients to whom a last observation carried forward approach was applied, the median improvement of the MADRS score was 48.0% (range –20.7%–100%), with 48.7% of patients considered responders, 23.1% partial responders and 28.2% non-responders. Median retention time was 8 weeks (range 2–34).

Conclusions: This algorithm-guided antidepressant treatment was acceptable for clinicians and resulted in an elevated final response rate among study completers. However, the dropout rate was high, mainly due to treatment interruption or non-observance.

Key words: depression; complete remission; algorithm; drug therapy

Introduction

Treatment protocols are now widely used in many medical specialities such as obstetrics, paediatrics and cardiology. In psychiatry as well, a great deal of attention has been given to the development of practice guidelines and medication algorithms for management of mental health disorders. Depression is a major public health problem for which effective pharmacological treatment is now widely available in outpatient and inpatient settings [1]. The aim of treatment is symptomatic remission and functional recovery [2], with maintenance treatment to prevent relapse [1]. Symptomatic improvement (i.e. response as defined as a ≥50% reduction of the initial score on a depression scale) is distinguished from remission (i.e. minimal or no symptoms) because remission, in contrast to a response with residual symptoms, is associated with better functioning and a better prognosis [3, 4]. Failure to achieve remission is frequently due to inadequate dosage, too short duration of treatment or insufficient use of the available therapeutic options in cases of partial remission [2].

Because treatment success is never guaranteed with any antidepressant, clinicians often use a sequence of treatment steps (either monotherapies or combinations) to increase the likelihood of remission. Recent efforts have aimed to define algorithms to operationalise these different steps [5–7].

In spite of a general consensus among experts concerning the pharmacological strategies to be used, a certain number of questions remain with little or no answer. Few data have been published on the effects of increased dosage in cases of non-response or partial response [8–10]. Moreover, the selective serotonin reuptake inhibitors (SSRIs) being now the first-line antidepressants, in cases where partial or complete remission is not achieved with such compounds the best strategy for obtaining remission has not been clearly de-

fined. Suggested methods have included another increase in SSRI dosage, administration of another antidepressant with a broader spectrum of action (a tricyclic or a serotonin noradrenaline reuptake inhibitor [SNRI]) or the addition of lithium or triiodothyronine [11–13].

On the basis of these considerations we developed an algorithm-guided treatment plan aimed at obtaining complete remission. The general principle of this systematic treatment algorithm is to progressively reinforce drug therapy where clinical response in outpatients with depressive episodes is wholly or partially lacking. The strategy selected can be called "semi-naturalistic", since it aims at combining a strict treatment algorithm with the daily complexity of clinical reality [8].

The main objective of the study was to describe the proportion of patients reaching complete remission at the different steps of a treatment algorithm, starting with the usual first intention treatment (daily defined dose of an SSRI) and ending with a tricyclic antidepressant and a double potentiation (lithium and triiodothyronine) for the most resistant patients. The second objective was to compare, at an intermediate level of the algorithm, several available options for SSRI non-responders. The third objective was to test the global feasibility of an algorithm of this kind in clinical conditions.

This paper reports the final findings of this semi-naturalistic study, which we have named the Geneva Outpatient Depression Study (GODS).

Methods

### Patient evaluation and selection

Over a 4-year period (1999–2002), all male and female patients admitted to our outpatient clinic in a university department of psychiatry (an outpatient clinic occupying a secondary rather than tertiary position in the local health system) with probable clinical diagnoses of depressive episodes were screened for inclusion and exclusion criteria. The diagnosis of the depressive episode and the comorbidities were screened by use of the M.I.N.I. (Mini International Neuropsychiatric Interview), ICD-10 version [14]. The potential presence of a borderline personality disorder was investigated by means of a checklist based on the corresponding DSM-IV-R diagnostic criteria. Severity of depression was assessed by trained senior residents or clinical research nurses using the Montgomery and Asberg Depression Rating Scale, MADRS [15].

To be included in the study outpatients had to meet the following requirements: age between 18 and 65 years; a moderate or severe depressive episode without psychotic characteristics as per the ICD-10 [16] (F.31: depressive episode, bipolar affective disorder; F.32: depressive episode; F.33: depressive episode, recurrent depressive disorder), and a minimum score of 25 on the MADRS scale [15]. For women of child-bearing age information was provided on the need for contraception. The exclusion criteria included the presence of one of the following diagnoses or criteria: (1) an organic illness (in particular cardiovascular, renal, hepatic or cerebral) contraindicating the use of the antidepressants or lithium or presenting a

Figure 1

Overview of number of complete remitters, responders, partial responders 1, partial responders 2, non-responders and dropouts during the different steps of the GODS protocol.

REM = Complete remitters (MADRS score <8 at two consecutive visits); RESP = Responders (MADRS reduction from baseline ≥50%); PR2 = Partial responders 2 (MADRS reduction 41 to 50%); PR1 = Partial responders 1 (MADRS reduction 26 to 40%); NR = Non-responders (MADRS reduction <25%); DO = Dropouts; Li = lithium; T3 = triodothyronine
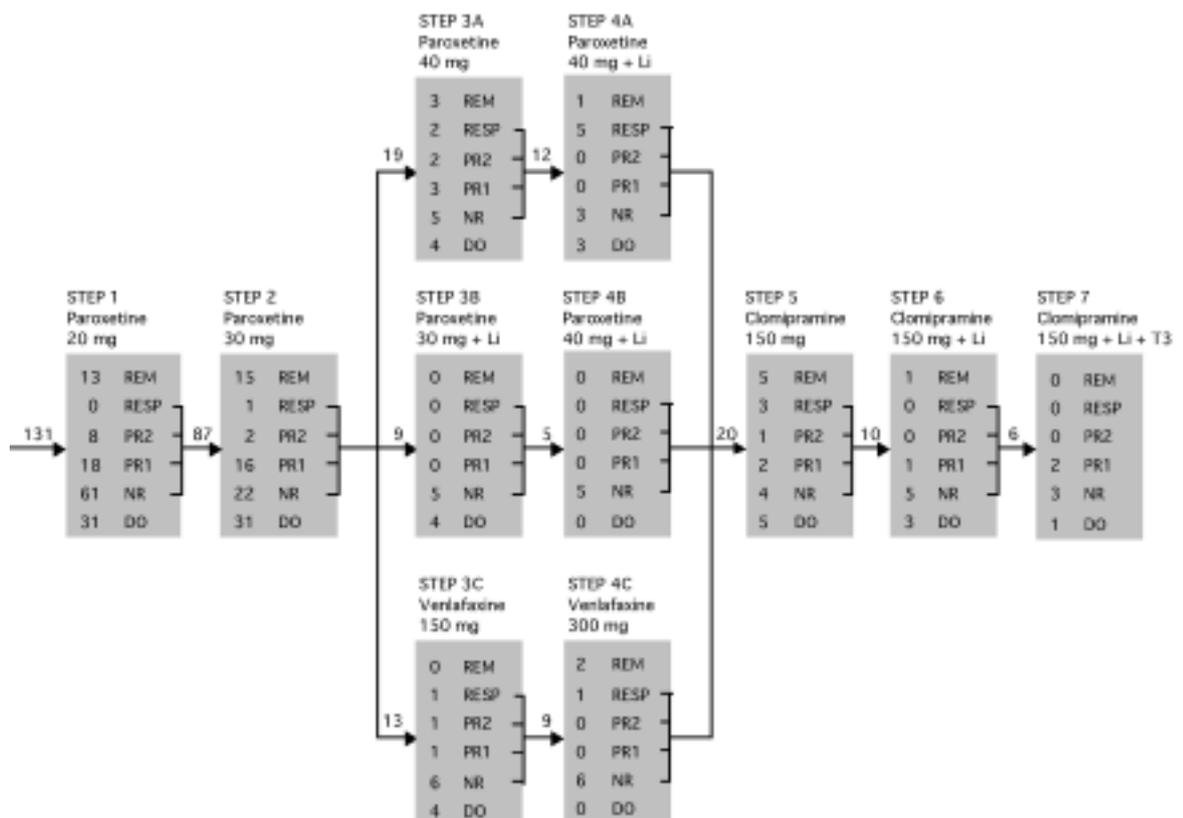
life-threatening condition; (2) pregnancy; (3) schizophrenia or schizoaffective disorder; (4) presence of psychotic characteristics (congruent or non-congruent with mood); (5) borderline personality disorder; (6) dependence on alcohol or other substances, as per ICD-10, during the preceding year; (7) hypersensitivity to one of the antidepressants used or to lithium; (8) failure of a previous treatment at minimun dosage over at least a 2-week period, with one of the antidepressants used in the study (paroxetine: 20 mg/day; venlafaxine 75 mg/day; clomipramine 150 mg/day); (9) MAOI or fluoxetine treatment during the previous two weeks; (10) mood-stabilising or antipsychotic treatment. If any antidepressants had been taken previously, the clinician evaluated the time needed after discontinuing this treatment before inclusion in the study.

The study was in conformity with the recommendations of the Declaration of Helsinki and received the approval of the Ethics Committee of the Geneva Department of Psychiatry. Patients gave their written informed consent.

The GODS treatment algorithm

The primary feature of the GODS treatment algorithm is a stepwise medication change based on the results of clinical evaluation with the MADRS at 2- or 4-week intervals according to the procedures for advancing from one step to the next (see below). The GODS consisted of up to 7 sequential treatment steps (step 1 to step 7) (figure 1).

The GODS algorithm defines *no response* to treatment as a reduction by 25% or less of the initial MADRS score, *partial response 1* as a reduction by 26% to 40%, *partial response 2* as a reduction by 41% to 50%, *response* as a reduction by 50% or more, and *complete remission* as a MADRS score of 8 or less.

The procedures specified that a move to the next step was warranted if a 25% decrease in the initial MADRS score *(partial response 1)* was not observed. Patients were assessed for possible progression to the next step every two weeks for steps 1–4 and every four weeks for steps 5–7. Once the 25% reduction was obtained, the goal shifted to a 40% reduction *(partial response 2)*. If this goal was not achieved at the next patient evaluation, the treatment was stepped up. If it was achieved, the treatment remained unchanged and the goal shifted to a 50% reduction *(response)*.

This approach was based on our clinical experience, supported by research [17, 18] showing a close correlation between the results obtained after one or two weeks and those obtained after 4 weeks.

Once the *response* was obtained (50% reduction or more of the initial score on the MADRS), the goal was to reach complete remission (MADRS score of 8 or less).

With this in view, the rules were modified to allow a slower progression. Patients remained with the same treatment if they continued to improve (i.e. one point mean decrease of the MADRS score between two consecutive visits). However, if there was a clear worsening (i.e. initial MADRS score/2 + 5 points) the patient moved to the next step.

Step 1 was based on the minimum effective dose of an SSRI, paroxetine 20 mg in the evening. If the response was inadequate, patients moved on to step 2, which corresponded to a higher dosage of 30 mg/day paroxetine. If complete remission was not obtained with paroxetine after steps 1 and 2, a crossroad (step 3) determined the therapeutic reinforcement by randomised allocation of three treatments: increased paroxetine dosage to 40 mg/day (step 3A), addition of lithium to paroxetine 30 mg/day treatment (step 3B) or switch to venlafaxine (extended release form) 75 and after two days 150 mg/day in the evening (step 3C). After one week, the lithium (lithium sulphate slow release) doses were adapted according to plasma levels to target blood lithium levels of 0.6–0.8 mEq/L.

If the clinical evolution was unsatisfactory, patients moved on to step 4. For those in step 3A, lithium was added to paroxetine 40 mg/day (step 4A); for those in step 3B, lithium was continued and paroxetine increased to 40 mg/day (step 4B); for those in step 3C, venlafaxine was increased to 225 and after two days to 300 mg/day (150 mg b.i.d.) (step 4C). Paroxetine 40 mg/day was estimated a sufficient dose, as no significant benefit was shown with dose escalation from 20 mg to 40 mg/day [8].

In the absence of clinical improvement, the next step (step 5) was tricyclic antidepressant treatment with clomipramine (slow release form). Progressive titration by 37.5 mg/day increments every two days continued until the final dose of 150 mg/day, taken once in the evening, was reached. After two weeks of treatment, the clomipramine dosage was adjusted according to the results of therapeutic drug monitoring (TDM). The targeted therapeutic windows for clomipramine and desmethyl-clomipramine were 50–150 and 50–300 ng/ml respectively.

If the response to this treatment was unsatisfactory, the following steps allowed for the addition of lithium to clomipramine (step 6) and finally, for patients still resistant to treatment, addition of triiodothyronine (T3: 37.5 mg/day taken in the morning) to the lithium and clomipramine regimen (step 7).

The comedications allowed were clorazepate, maximum 30 mg/day, for anxiety and zolpidem, maximum 20 mg/day, for insomnia. In addition to the psychological support provided during the fortnightly visits, a number of psychosocial services were offered to reduce dropouts and encourage patient participation in treatment. These included group support sessions for depressive patients (daily then weekly), psychoeducation groups on depressive disorders and their treatment, and regular discussions with the nurse about the importance of medication compliance. When, after inclusion of the first 50 patients, a high rate of non-compliance was observed, nurse phone calls were added to these services during the week to remind patients of appointments and treatment.

TDM was carried out after the first two weeks of therapy with paroxetine, venlafaxine and clomipramine and was repeated two weeks after a change in dosage and after prescription of lithium for adaptation of plasma levels. Thyroid function (TSH and T4L) was assessed as routine screening at inclusion. When lithium was added further tests were carried out (creatinine, Na+, K+, T4L, TSH and ECG). Before and after the addition of triiodothyronine a further evaluation of thyroid function was performed including T3L, T4L and TSH.

Statistical analysis

Descriptive statistics included frequencies and percentages for categorical variables and median and range for continuous variables. Subgroups of patients considered to be dropouts and study completers were compared with the Fisher exact test for categorical variables and the Mann-Whitney U-test for continuous variables. The MADRS decrease at each step of the treatment algorithm was tested using the Wilcoxon signed ranks test. Statistical analysis was performed with the SPSS package, version 11 (SPSS Inc., Chicago, IL). The significance level was set at 0.05 (two-sided tests).

Results

A total of 135 patients gave informed consent and entered the study. Of these, 4 patients were subsequently excluded because of major protocol violations. The descriptive and efficacy analyses were thus conducted with a sample of 131 patients. Sociodemographic and clinical characteristics of the study population are presented in table 1. Median numbers of previous depressive episodes and suicidal attempts were 1 (range 0–8, n = 118) and 0 (range 0–3, n = 105) respectively. Median duration of the current depressive episode at inclusion was 8 weeks (range 2–52).

The comedications allowed (clorazepate and zolpidem) were used by 79 out of the 121 patients for whom data were available.

Figure 1 presents an overview of the number of complete remitters, responders, partial responders 1 and 2, non-responders and dropouts during the different steps of the GODS 1 treatment algorithm. The dropouts were divided into two subgroups according to the reasons of non-completion: withdrawals were patients who spontaneously decided to withdraw from the study (mainly through repeated missed appointments) and exclusions were patients excluded by the investigators because of non-compliance (as shown by TDM), adverse effects or other reasons (table 2).

Overall attrition

Overall, 66% (n = 86) of the patient sample dropped out of the study, with 44% (n = 57) excluded by the investigators and 22% (n = 29) withdrawn because of patient decisions to discontinue (table 2). Prevalence of non-compliance, as

Table 1

Clinical and socio-demographic characteristics of the patients (n = 131).

		N	%[1]
Gender	Female	78	60
	Male	53	41
Age (median, range)		35	(19–62)
Marital status (n = 115)	Single	31	24
	Married	48	37
	Divorced	25	19
	Separated	10	8
	Widowed	1	1
Relevant medical history	History of depression (n = 124)	77	54
	Previous antidepressant treatment (n = 129)	34	26
Diagnosis (ICD-10)	F31.4	8	6
	F32.2	46	35
	F33.2	77	59
Associated diagnoses (MINI)			
Anxiety disorders	Generalised anxiety disorder	47	36
	Panic disorder	9	7
	OCD	2	2
	Phobia	14	11
	Unspecified	4	3
	>One anxiety disorder	29	22
Substance abuse	Alcohol	17	13
	Cannabis	1	1
	Alcohol and cannabis	4	3
	Unspecified	4	3

[1] Percentages are calculated on the whole sample (n = 131)
Abbreviations:
ICD-10: International Classification of Diseases, 10th revision
MINI: Mini International Neuropsychiatric Interview
OCD: Obsessive-compulsive disorder

Table 2

Distribution of dropouts from the study (n = 131).

	N	%[1]
Total dropouts	86	66
Exclusions (Investigator's decision to exclude the patient)	57	44
For non-compliance documented from TDM	18	14
For adverse effects	27	21
For other reasons[2]	12	9
Withdrawals (Patient's decision to interrupt treatment and follow-up)	29	22
With non-compliance documented from TDM	12	9
Without non-compliance documented from TDM	17	13

[1] Percentages are calculated on the whole sample (n = 131)
[2] These included mixed state (n = 2), somatic illness (n = 1), change in diagnosis (n = 7) and suicidal attempt (n = 2). TDM = therapeutic drug monitoring.

Table 3

MADRS scores and changes at each step.

	Na	MADRS score Median [min-max]	MADRS change from baseline[b] (%) Median [min-max]	MADRS change at each step[c] (%) Median [min-max]
Baseline	131	33 [25–49]		
End of step 1	117	25 [0–42]	23 [–23–100]	23 [–23–100]
End of step 2	69	23 [0–38]	33 [–19–100]	10 [–88–100]
End of step 3A	18	21 [6–36]	39 [–3–82]	17 [–44–81]
End of step 3B	6	32 [12–42]	10 [–20–57]	–2 [–45–43]
End of step 3C	12	22 [13–37]	24 [–12–58]	7 [–67–40]
End of step 4A	11	16 [4–38]	52 [–9–87]	7 [–44–81]
End of step 4B	5	32 [27–43]	6 [–16–16]	–2 [–33–25]
End of step 4C	9	24 [6–34]	19 [–22–86]	0 [–50–77]
End of step 5	18	16 [2–37]	54 [–21–93]	44 [–17–91]
End of step 6	9	26 [6–37]	21 [0–80]	–25 [–146–70]
End of step 7	5	34 [17–40]	3 [–8–37]	–6 [–40–32]
End of study (LOCF)	117	16 [0–40]	48 [–21–100]	

[a] Number of patients with at least 2 MADRS evaluations two weeks apart at a given step
[b] MADRS change from baseline = 100 X [MADRS at baseline – MADRS at step exit] / MADRS at baseline
[c] MADRS change at each step = 100 X [MADRS at step entry – MADRS at step exit] / MADRS at step entry
LOCF = last observation carried forward approach

documented from measured plasma levels, was 23% (n = 30).

In an exploratory perspective, factors possibly associated with dropout were investigated by comparing dropouts (n = 86) with study completers (n = 45) who either achieved remission (n = 40) or completed the 7 steps without remission (n = 5). The only factor significantly associated with dropout was shorter duration of the depressive episode at admission (median, range: 5 weeks, 2–52 versus 12 weeks, 4–34; Mann-Whitney U-test, p <0.001). Groups did not significantly differ with respect to gender, age, history of depression or associated diagnoses of anxiety disorders or substance abuse.

In an attempt to reduce attrition and noncompliance rates, nurse phone calls were introduced to remind patients of treatment and appointments. However, when comparing patients contacted by phone (n = 81) with those who were not (n = 50), dropout rates did not significantly differ (64.2% versus 68.0%, Fisher exact test, N.S.). Rates of non-compliance also remained similar (24.7% versus 20.0%, Fisher exact test, N.S.).

Overall response

Of the 131 patients entering the protocol at step 1, 45 were considered to be study completers. Forty patients were complete remitters (30.5%), with a median time before achieving remission of 10 weeks (range 4–34). Five patients had not reached remission at the end of the 7 steps of the protocol.

The 117 patients who had at least one MADRS assessment after inclusion were further considered in a last observation carried forward approach for the overall treatment algorithm. The median MADRS score decreased from 33 (range 25–49) at inclusion to 16 (range 0–40) at discharge from the study. Median improvement of symptom severity was 48.0% (range –20.7–100%), with 48.7% of patients considered to be responders, 23.1% partial responders and 28.2% non-responders. Median study retention time was 8 weeks (range 2–34).

MADRS scores at the end of each treatment step, change within a given step and improvement from baseline score are documented in table 3.

Discussion

The three main aims of this study were to evaluate, among severe depressive outpatients, the proportion of patients obtaining complete remission at the different steps of a medication algorithm; to compare, at an intermediate level of the algorithm, several of the options available when a patient did not respond to the SSRI that was used as a first-intention antidepressant; and to test the feasibility of the algorithm in clinical practice and in the conditions of an open seminaturalistic design.

In the light of the results we must, before considering these three aims, emphasise the fact that the most significant finding in this trial is the high attrition rate, with 66% of the sample not completing the study. Non-compliance, as measured by plasma levels, was the most common factor associated with dropout (23%), including patients

who withdrew and those who were excluded. The other common causes of dropout were treatment-induced, unbearable side effects (21%) and self-withdrawal without TDM evidence of non-compliance (13%). A review of controlled therapeutic studies suggests a dropout rate of up to 33% irrespective of antidepressant drug class [11], but higher rates are observed in clinical practice [19]. In general, between 30% and 60% of all patients fail to take medication they have been prescribed and compliance in psychiatric patients seems comparable with other patient populations [20]. Consequently, adherence to treatment with antidepressant drugs is an issue of major clinical relevance.

The factors leading patients to discontinue therapy, as well as the issue of what specific interventions contribute to improving adherence, are not fully understood [19]. The two reasons that have been most frequently examined in clinical trials are lack of efficacy and adverse events. However, a small study by Maddox et al. [21] revealed that the reasons for dropping out are different in naturalistic settings. In this study, feeling better was the most frequent reason given, followed by adverse events, other reasons, physician's instructions and non-response to medication. In our study, the only factor affecting attrition was shorter length of the current depressive episode, which has already been shown to affect adherence [20].

It is worth noting that placebo response is also associated with shorter episode duration in placebo-controlled trials [22–25]. Thus, spontaneous improvement in individuals with short episode duration may have contributed to the high attrition rate. However, no data are available about the reasons behind non-compliance in our trial. Moreover, our intervention (nurses' phone calls) aiming to reinforce and improve patient adherence and reduce dropouts had no effect. An intervention of this kind was probably not forceful enough to improve treatment adherence [26]. Even if patients were encouraged to take advantage of several supportive and psychoeducational activities in our protocol, no formal structured psychotherapy was offered. This may have contributed to the present study's significant dropout rate, as psychotherapy may have a possible adherence-enhancing role [27].

The first consequence of the high attrition rate is that only 30.5% of the patients who entered the GODS study reached full remission. These findings correspond to those of other naturalistic and general effectiveness studies [5, 28–30]. However, as a result of this high attrition rate, the first aim of the study (evaluation of the proportion of patients obtaining complete remission at the different steps of a medication algorithm) was only partly accomplished. Nevertheless, it is worth noting that two-thirds of the patients in this trial achieved complete remission with paroxetine 20 mg and 30 mg in monotherapy, during steps 1 (n = 13: 9.9%) and 2 (n = 15: 17.2%) respectively.

Furthermore, although there is overwhelming evidence that lithium augmentation of antidepressants is an effective strategy for treating non-responders and/or resistant patients [31], the remission rates did not greatly increase after lithium augmentation of paroxetine in our trial, since only 1 out of 21 patients improved. This is much lower than the response rate reported for lithium addition in SSRI non-responders [13, 32], even if this rate is usually lower than for lithium addition to tricyclic non-responders. Moreover, only one of the 10 clomipramine non-responders reached complete remission after lithium addition. However, it should be stressed that most of the patients who received clomipramine were already resistant to lithium augmentation (addition to paroxetine at steps 4A, 3B and 4B).

When investigating which treatments provided the greatest number of complete remissions (in relation to the number of patients entering the step), the best results were obtained with venlafaxine (300 mg) (2/9) and clomipramine 150 mg (5/20), which are potent multi-action antidepressants at such doses. This finding may provide further evidence of the relative advantage of such agents in achieving remission among both in- and outpatients [33–35].

It is worth noting that the 40 complete remitters participated in the study for a relatively long period of time (median 10 weeks; range 4–34), especially considering the fairly aggressive treatment plan. Moreover, when considering the GODS study completers, 88% (40/45 patients) reached complete remission. The main reason for the very favourable outcome among the study completers may be the fact that the study period was not limited as in most RCT's, but continued until either full remission or the end of the algorithm. Another reason for these favourable results may be the exclusion of those patients presenting a borderline personality disorder who may have a more treatment-refractory course of illness [36]. Finally, we cannot exclude the possibility that individuals with potential drug resistance were over-represented among the dropouts.

The high attrition rate also significantly affected the second objective of the study, since the number of subjects who reached steps 3 and 4 was too small for a statistical comparison of the three therapeutic arms: venlafaxine 150 and then 300 mg, paroxetine 40 mg, and paroxetine 40 mg + lithium. Moreover, at step 3 randomisation was only partial. For practical reasons (time pressure in clinicians' daily activities), a subgroup of patients received a paroxetine dose increase (corresponding to the 3A arm) without being randomised. This resulted in an unbalanced, incompletely randomised arms allocation with a clear excess of patients in the 3A arm. Consequently, the second objective (i.e. to compare three treatment options for SSRI non-responders) was not attainable.

The third objective of this trial was to determine the feasibility of an algorithm of this kind in

clinical practice. Overall, patient acceptance of the GODS protocol was fairly satisfactory. Our experience with the clinicians was more mitigated, since acceptance was only partial among the young clinicians. After one year we selected a more limited number of clinicians. As a result, their acceptance of and compliance with the protocol improved. Furthermore, seven steps were probably too many and randomisation could not always be appropriately carried out in this naturalistic clinical context. On the other hand, the clinicians easily assimilated the relatively complex rules guiding decisions. Such rules greatly contributed to homogenisation of therapeutic decisions in the course of treatment.

In conlusion, the present study has confirmed that many patients do not continue their treatment and/or take the prescribed drug treatment, and that an SSRI as first intention treatment followed by the possible use of a multi-action antidepressant (including tricyclics) may be useful in the event of resistance.

Moreover, simply exposing physicians to a treatment algorithm may not be sufficiently effective in the treatment of a major depressive disorder. It may be of particular interest to study the long-term outcomes of patients who dropped out of treatment (with special attention to the risk of suicide, chronicity, and inability to work, a highly sensitive topic in Switzerland). This may make it possible to evaluate the needs of such patients and design appropriate strategies to reduce the number of such dropouts, including patient education programmes and integration of structured elements of psychotherapy.

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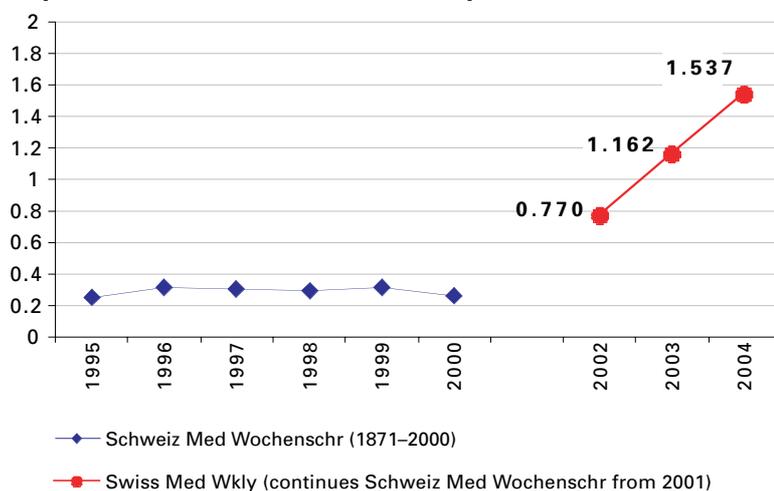
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