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Full Length Research

Treatment-resistant depression amongst older adults: Risk factors and treatment options

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Depression is one of the most common mental health disorders of the elderly. Though depression is a treatable condition, approximately one-third of patients do not respond to treatment and fall into the category of 'treatment resistant depression' (TRD). The aim of this paper is: (1) to investigate the definition for TRD, (2) to review the risk factors that contribute to TRD in later life and (3) to describe the treatment options for TRD in later life. Electronic MEDLINE literature search (Ovid) from 1981 to 2002 using the key words 'treatment resistant depression' and 'elderly' was carried out. Additional relevant articles cited by the retrieved papers were manually searched and screened to ensure that they met the following inclusion criteria: (1) use of an acceptable diagnostic criteria for depression, (2) TRD defined as failure to respond to one or more adequate trials of antidepressant for at least 6 weeks, (3) participants' mean age of 60 years or more and (4) sample size of at least 10 subjects. The concept of TRD remains contentious and poorly defined. Few cross-sectional studies have systematically investigated the risk factors associated with TRD. At present, there are no well-conducted randomised trials investigating how best to treat older adults with TRD. TRD in later life remains poorly defined and understood. There is an urgent need for the introduction of a widely accepted definition of Treatment Resiatant Depression, as well as the reliable identification of populations at risk and development of evidence-based treatment algorithms for patients.

Key words: Depression, elderly, treatment resistance, treatment refractory, management, risk factors.

INTRODUCTION

Depression is common in later life and the number of older adults with depression will continue to increase as this segment of the population grows (Snowdon, 1990). The World Health Organisation estimated that by the year 2020, over one billion people will be aged 60 years or over and this age group will represent approximately 10% of the entire world's population. If one takes into account the fact that depression affects approximately 10% of community living older adults (Copeland et al., 1987), then the size and the challenge we are about to face becomes apparent. Fortunately, antidepressant medications are now widely available and 60 - 80% of older adults with depression show good response to standard treatment (Mittmann et al., 1997). However, these encouraging results also reveal a contrasting and sombre reality: 20 - 40% of older adults with depression do not adequately respond to antidepressant treatment and fall into the category of 'treatment resistant depression' (TRD) (Fava and Davidson, 1996; Baldwin, 1996). Of note, patients with TRD account for more than half of the total annual cost associated with the treatment of depression (Borrows et al., 1994).

Although TRD is relatively common, its concept remains contentious. The most simplistic definition of TRD is failure to achieve and sustain normal mood after adequate antidepressant treatment. Thase and Rush (1995) introduced a more complex 5-stage model based on prior treatment: (0) no single adequate trial with antidepressants; (1) non-response to one adequate trial with a selective serotonin reuptake inhibitor (SSRI), tricyclic (TCA) or heterocyclic antidepressants (HCA); (2) non-response to two adequate trials of antidepressants from different classes; (3) stage 2 plus failure to respond to one augmentation therapy; (4) stage 3 plus failure to respond to two augmentation strategies and (5) stage 4 plus failure to respond to electroconvulsive therapy. More recently, after taking into consideration key-issues such as correct diagnosis, adequacy of treatment and number of failed therapeutic trials, Souery et al. (1999) proposed that TRD can be defined as a 'major depressive episode

with poor response to two adequate trials of different classes of antidepressants for a mean duration of 6 to 8 weeks'. However, there is no universally accepted definition of TRD and to our knowledge, information about the issue of TRD in later life has not as yet been comprehensively investigated.

This paper aims to review the definitions of TRD, the clinical factors that may significantly contribute to increase the risk of TRD, as well as the most effective strategies to improve treatment response of older adults with TRD.

METHODS

This review involved a detailed evaluation of the literature published in the area of treatment- resistant depression from 1981 to 2002. The literature search was based on the MEDLINE (Ovid Database) and used the following search strategy: (1) "depression" or "depressive disorder" or "major depression" or "depressive episode" or "dysthymia", (2) "treatment resistance" or "treatment refractory" or "treatment non-response", (3) "aged" or "aging" or "late life" or "later life" or "geriatric" or "elderly", (1) and (2) and (3). In addition, a manual search of relevant articles cited by papers retrieved during our initial electronic search was undertaken. All retrieved articles were then screened to ensure that they met the following criteria:

1. Use of accepted diagnostic criteria for depression according to DSM-III, DSM-III-R, DSM-IV, ICD-9, ICD-10, or Research Diagnostic Criteria (RDC).
2. TRD defined as failure to respond to one or more adequate trials of antidepressant medication in relation to dosage and duration of treatment (6 weeks or more).
3. Subjects aged 60 years and over or sample's mean age equal or greater than 60 years.
4. Minimum sample size of 10 subjects.
5. Published in English.

A total of 165 papers were retrieved by the electronic (108) and manual (57) search. Sixty-two had to be excluded because subjects' mean age was lower than 60 years, 40 did not describe an acceptable definition of TRD, 19 were case-reports and provided information on less than 10 cases and 34 papers were editorial comments or reviews. Finally, only 10 studies met the inclusion criteria set out for this review (Hsieh et al., 2002; Lenze et al., 2001; Simpson et al., 2001; Little et al., 1998; Simpson, 1997; Bonner and Howard, 1995; Stoudemire et al., 1993; Pinto et al., 2002; Weintraub, 2001; Zimmer et al., 1991).

RESULTS

Definitions of TRD

As one of the aims of the present study was to evaluate the definition of TRD in later life, all reports outlining criteria for TRD were included in this part of the review, regardless of whether they met all the inclusion criteria outlined above. Forty-four reports explicitly described how TRD was defined. Only 10/44 studies used 6 or more weeks of antidepressant treatment as a necessary requirement for the definition of TRD. Sixteen papers required 8 or more weeks of treatment to characterise TRD. Few trials mentioned the required dosage of the medications used and there was considerable heterogeneity as to what 'response to treatment' actually meant (that is, decline in the severity of depressive symptoms, 50% reduction in the severity of depressive symptoms, full clinical recovery). Twelve reports did not offer sufficient information to enable them to be classified according to Thase and Rush's criteria, 12/44 met criteria for stage 1, 17/44 criteria for stage 2 and 3/44 for stage 3 or more. Overall, only 20/44 provided sufficient information to establish the diagnosis of TRD according to Thase and Rush's criteria (Table 1).

Risk factors

Information about the factors that lead to TRD remains relatively sparse and is mostly based on the results of cross-sectional studies (Table 2). Overall, they suggest that TRD in later life is associated with increased brain pathology (both cerebral atrophy and subcortical disease), older age, greater chronicity of physical illness and poor social support, but due to the limited number of papers and likely publication bias, no firm conclusions can be drawn at this point of time about the most relevant risk factors for TRD in later life.

Treatment options of TRD among the elderly

Although many reports have been published describing different clinical strategies to manage TRD, few have explored this issue systematically in later life. The results of the 3 studies that met criteria for inclusion in this review are summarised in Table 3. They all reported data on case-series of TRD patients who were treated in an open-label fashion. The approach to the management of TRD varied, so that no firm conclusions can be reached regarding the most effective strategy to treat older adults with TRD.

DISCUSSION

The most important finding of this review is that TRD in later life remains poorly understood and under-researched. This is, alarmingly, happening on a background of a demographic revolution and an ever-increasing population of older adults at risk of depression. It is estimated that by 2020 the world will have over 1 billion older adults. 100 million are likely to display clinically significant depressive symptoms and of those, at least 20 million will be treatment-resistant. The personal and social cost associated with this potential epidemic cannot be easily dismissed. It is vital therefore, that a clear understanding of what TRD actually is as well as what can be done to treat it effectively be developed.

It was observed in this review that the term TRD has

Table 1. Definitions of TRD adopted by various studies.

Author	Mean age 60 years old	Duration	Antidepressants	Augmentation	ECT	Psychotherapy	Thase and Rush Stage
Hsieh et al., 2002*	Yes	12 weeks	Naturalistic treatment with either antidepressant monotherapy (53/60) or combination (7/60) of antidepressants.	–	–	–	NA
Montoya et al., 2002	–	–	Failed to respond to exhaustive pharmacotherapeutic agents	–	–	Yes	NA
Pinto et al., 2002*	Yes	6 weeks	1 trial of tricyclic or tetracyclic antidepressant and a trial of SSRI	–	–	–	2
Dursun et al., 2001	–	6 months	3 different antidepressants (2 from SSRI and 1 from TCA) at therapeutic dose	Augmentation with lithium, T3 and bupropion	Yes	–	5 or NA
Lenze et al., 2001*	Yes	26 weeks	Nortriptyline	Augmentation pharmacotherapy	–	Interpersonal therapy	NA
Sacheim et al., 2001a	–	6 weeks	2 or more antidepressants from different classes at adequate dose.	–	–	Yes	2
Simpson et al., 2001*	Yes	12 weeks	1 antidepressant medication	Augmentation with lithium	Yes	–	NA
Sacheim et al., 2001b	–	6 weeks	2 or more antidepressants from at least 2 different classes with adequate dose.	–	–	Yes	2
Weintraub, 2001*	Yes	8 weeks	Received antidepressants from two different classes at adequate doses & if their depression deemed severe.	–	–	–	1
Dalton et al., 2000	–	8 weeks	1 antidepressant medication	–	–	–	1
Maeda et al., 2000	–	6 weeks	3 different antidepressants at sufficiently high dose	–	–	–	NA or 2
Prochazka et al., 2000	–	–	2 different antidepressants at adequate doses.	–	–	–	2
Rush et al., 2000	–	6 weeks	2 or more antidepressants from different classes at adequate dose.	–	–	–	2 or NA
Montigny et al., 1999	–	8 weeks	1 antidepressant at therapeutic dose from: SSRI, TCA, HCA, MAOI classes	–	–	–	1
Rudas et al ., 1999	–	8 - 12 weeks	1 or more antidepressants from different classes at adequate dose	Augmentation with lithium or carbamazapine	–	–	3 or NA
Rybakowski et al., 1999	–	–	2 adequate trials with antidepressants from different classes (Thase & Rush)	+	Yes	–	5
Sajatovic et al., 1999	–	6 weeks	TCA at 50 - 150 ng/ml or fluoxetine 40 mg/d or sertraline 200mg/d	–	–	–	1

Table 1. Contd.

Bauer et al., 1998	–	–	Trial with several therapeutic and/or prophylactic agents	–	–	–	NA
Landen et al., 1998	–	4 weeks	Citalopram or paroxetine	–	–	–	1
Little et al., 1998*	Yes	13.7 to 26 weeks	Nortriptyline at steady state plasma levels of (80 - 120 ng/ml)	Augmentation with lithium, perphenazine, paroxetine, methylphenidate or lorezepam.	–	Yes	NA
Maes et al., 1998	–	–	2 adequate trials with anti-depressants from different classes (Thase & Rush)	+	Yes	–	5
Folkerts et al., 1997	–	8 weeks	2 different antidepressants (including at least one TCA) at a dosage of at least 100mg imipramine equivalent	–	–	–	2
Maes et al., 1997a	–	–	2 adequate trials with anti-depressants from different classes (Thase & Rush)	+	Yes	–	5
Maes et al., 1997b	–	–	2 adequate trials with anti-depressants from different classes (Thase & Rush)	+	Yes	–	5
Maes et al., 1997c	–	–	2 adequate trials with anti-depressants from different classes (Thase & Rush)	+	Yes	–	5
Moreno et al., 1997	–	8 weeks	2 adequate trials with anti-depressants from different classes (Thase & Rush)	+	Yes		5
Simpson, 1997	Yes	12 weeks	At least 1 antidepressant medication without clinical benefit	–	–	–	1
Hunsel et al., 1996	–	–	2 adequate trials with anti-depressants from different classes (Thase & Rush)	+	Yes	–	5
Maes et al., 1996	–	–	2 adequate trials with anti-depressants from different classes (Thase & Rush)	+	Yes	–	5
Bonner and Howard, 1995*	Yes	6 weeks	150 mg of imipramine or its equivalent	Augmentation with Lithium	Yes	–	NA
Stabl et al., 1995	–	9 weeks	Refractory to at least 2 previous treatments at adequate doses (150mg/d or more of TCA)	–	–	–	2
Bodkin et al., 1994	–	12 weeks	Adequate trials with anti-depressants from at least 2 different classes (TCA, MAOI, SSRI, etc.)	–	–	–	2
Nierenberg et al., 1994	–	6 weeks	3 different antidepressants from 2 different classes (TCA, SSRI, MAOI, atypical)	One augmentation with lithium or thyroxine or carbamazapine	Yes	–	NA

Table 1. Contd.

Voltz et al., 1994	_	3 weeks each	At least 2 classes of anti-depressants (except MAOI) at an adequate dose	_	_	_	2
Wilhelm et al., 1994	_	4 weeks	Adequate trials with TCA at 150mg/d imipramine or its equivalent, or MAOI: phenelzine 60mg/d or tranylcypromine 40mg/d	_	Yes	_	NA
Stoudemire et al., 1993*	Yes	6 months	Subjects received TCA or SSRI and switched either one	Lithium augmentation in selected cases	Yes	_	NA
Zimmer et al., 1991*	Yes	6 weeks	At steady state nortriptyline plasma level of (50 - 150 ng/ml)	Augmentation with Lithium	_	_	NA
Price et al 1990	_	_	Unresponsive to heterocyclic antidepressant during the current episode	_	_	_	I
Amsterdam and Berwish, 1989	_	_	Repeated nonresponse to prior antidepressant treatment during the current episode.	_	_	_	NA
Carl et al 1988	_	8 weeks	Adequate in-patient drug therapy.	_	_	_	NA
MacEwan and Remick, 1988	_	_	2 different antidepressants or an antidepressant and/or ECT	_	Yes	_	NA
Charney et a., 1986	_	_	Nonresponse to standard antidepressant treatments	Augmentation with lithium	Yes	_	NA
Zohor et al., 1985	_	6 weeks	TCA at doses not less than 150 mg/d imipramine or its equivalent	_	_	_	I
Heninger et al., 1983	_	3 weeks	TCA like amitriptyline or desipramine or with mianserin	_	_	_	I

* = Studies included in this review; NA = Not available/does not fit into any one of the Thase and Rush stage 1 – 5; SSRI - Selective serotonin reuptake inhibitor; TCA - Tricyclic antidepressants; MAOI = Monoamineoxidase inhibitors; ECT= Electro convulsive therapy.

been used in a variable and inconsistent way (Ananth, 1998). According to the International consensus group for the definition of TRD, failure to respond to two successive adequate antidepressant agents of different classes after a period of 6 to 8 weeks each defines TRD (Souery et al., 1999). This review showed that only 44/165 papers retrieved explicitly reported how TRD was defined, although in the majority of studies such a definition was not consistent with recommended criteria. However, it is also important to note that even widely accepted criteria of TRD, such as the one proposed by Thase and Rush, do not provide clear guidelines on practical clinical issues such as the dosage and duration of each trial of antidepressant or augmentation agent. Some might consider TRD as no response to a high dosage of antidepressant for 12 weeks (Moreno et al., 1997), while others would consider TRD as non-response to a trial using a standard dosage of antidepressant for 6 weeks (Pinto et al., 2002). Recent guidelines released by the Massachusetts general hospital for the staging of TRD included both the number of failed trials as well as intensity/optimisation of each trial (Fava, 2003), which represents a welcome attempt to establish a more systematic approach to the treatment of

Table 2. Risk factors of TRD among the elderly.

Author	Duration of index trial	Type of study/ intervention	Subjects	Outcomes	Definition	Thase and Rush Stage
Hsieh et al., 2002	12 weeks	Longitudinal study of the relationship between treatment response and hippocampal volume in a naturalistic treatment milieu with either monotherapy (53/60) or combination (7/60) of antidepressants.	Responders = 22 Non-responders=38 M:F = 24:36 Mean age 68.57 ±6.43	No significant difference sociodemographic variables except that non-responders were more likely to be older. Non-responders showed reduction in both right hippocampal and total hipocammpal volume in the lowest 25th. percentile.	Failure to show reduction in MADRS score < 9 after 12 weeks of treatment with antidepressant.	-
Lenze et al., 2001	26 weeks	Longitudinal study of treatment outcomes and subjective health measures. Patients were given an antidepressant, interpersonal therapy and augmentation pharmacotherapy.	Responders = 134 non-responders = 16	TRD had significantly greater personality pathology and greater IADL disabilities. Poor self-rated health predicted non-response to treatment.	Failure to show decrease in HRSD < 10 after 26 weeks of treatment with an antidepressant, augmentation pharmacotherapy and interpersonal therapy.	_
Simpson et al., 2001	6 months	Cross-sectional study of regional cerebral volume measurements and treatment response in late life depression. Subjects received an antidepressant and lithium augmentation or ECT.	Responders = 33 non-responders =11	No association was observed with age, age at onset of first depressive episode or with severity of depression. TRD group had significantly poor physical health and were from lower social class. Poor physical health was associated with reduced frontal, parietal & temporal lobe volumes. Poor physical health, later age at onset of 1st. episode of depression and previous use of ECT predicted larger lateral ventricular volume.	Failure to achieve MADRS score of < 10 at 6 months with an antidepressant treatment and second line treatment (lithium augmentation or ECT)	_

Table 2. Cont'd.

Little et al., 1998	19 weeks	Naturalistic case series study to elucidate the frequency of TRD among the elderly. Subjects received nortriptyline upto steady state levels 80-120 ng/ml, adjunctive pharmacotherapy and inter-personal psychotherapy	Responders = 119 non-responders = 28 Mean age 67.6+_5.8	TRD were more likely to be older, living alone and divorced or separated. Rate of adjunctive pharmacotherapy was significantly higher among the TRD.	TRD was defined as lack of response to nortriptyline, augmentation agents and psychotherapy.	_
Simpson, 1997	12 weeks	Cross-sectional case series study of cerebral pathology in elderly patients with TRD. Subjects were treated with at least one type of anti-depressant.	14 cases of TRD M:F = 4:10 Mean age 68+_7.9 (range 58 -84)	Subcortical vascular pathology was seen in 6/14 and cerebral atrophy in 4/14 of the subjects with TRD using CT or MRI. Cerebral abnormalities were noted on SPECT in 9/14 subjects.	Subjects treated with at least one type of antidepressant for at least three months without clinical benefit.	Stage 1
Bonner and Howard, 1995	6 weeks	Retrospective evaluation of clinical characteristics among the elderly with TRD. Subjects were prescribed with adequate dose of antidepressants, at least 150 mg of imipramine or its equivalent with Li and ECT.	Responders = 30 non-responders = 29	TRD had significantly more previous admissions, spent longer time in hospital and had onset of depression before 50 years of age. Significant number of subjects with TRD had hypochondriacal symptoms, showed evidence of cognitive impairment, often prescribed benzodiazepines and less likely to receive ECT.	Continue to present with clinical features of depression despite of adequate treatment with antidepressants (at least 150 mg of imipramine or its equivalent) for at least six weeks with Li and ECT	Stage 1
Stoudemire et al., 1993	6 months	Longitudinal study on treatment outcome of elderly with TRD up to 4 years. Subjects received TCA or SSRI and switched either one with additional ECT or Li.	Responders = 37 non-responders = 17	No significant difference in age, level of education, severity of baseline depression or cognitive impairment was noted between TRD and treatment response group.	Failed to demonstrate clinically meaningful improvement (HAMD < 13 or > 50% reduction) with an antidepressant or ECT at 6 months.	_

IADL = Instrumental activities of daily living; MADRS= Montgomery asberg depression rating scale; HRSD - Hamilton rating scale for depression; HAMD - Hamilton rating scale for depression; ECT - Electroconvulsive therapy.

Table 3. Treatments described for the management of TRD among the elderly.

Author	Duration of index trial	Type of study/ intervention	Subjects	Outcomes	Definition	Thase and Rush Stage
Pinto et al., 2002	6 weeks	Retrospective study of case series using venlafaxine (150 - 375mg/day) in combination with ECT (6 - 12) in TRD	TRD = 13 M:F = 3:10 Mean age 62+_11.3 (range 34-75)	10/13 subjects responded to treatment showing improvement on CGI score of very much improved and much improved. Significant improvement in HAMD score (> 50%) was observed. Asystole was noted in 4/13 patients at higher doses of venlafaxine >300 mg/day.	TRD was defined as non-response to a trial of TCA and SSRI for at least 6 weeks.	-
Weintraub, 2001	2-year	Case series study of nortriptyline in geriatric depression resistant to Serotonin Reuptake Inhibitor (SRI). Subjects received nortriptyline if they had already received antidepressants from two different classes at adequate doses & if their depression deemed severe.	TRD = 10 M:F = 2:8 Mean age 76.8+_10.7 (65 -93)	7/10 subjects responded to addition or substitution of nortriptyline and were rated as very much improved and much improved on the CGI-Improvement Scale. All 7 responders were maintained on nortriptyline without relapse or recurrence of depression at a mean duration of 59.4 weeks+_27.7 (range 30 - 96 weeks)	Resistant depression was defined as having complied with and failed to respond to at least an 8-week trial of an SRI prescribed or another antidepressant from different class above the minimum recommended dose.	Stage 2
Zimmer et al., 1991	6-week	Case series involving open trial of Lithium (300 - 450mg/day) augmentation in patients who failed to respond to nortriptyline	Li augmentation = 11 M:F = 3:8 Mean age 74.1+_8.2 (range 59 - 89)	9/11 showed significant reduction on HAMD score (from mean score of 24.7+_5.9 to 16.4+_6.8) after augmentation of nortriptyline with lithium was initiated.	Failure to respond to a steady state plasma nortriptyline level of 50 - 150 ng/ml for a period of 6 weeks.	-

CGI = Clinical global impresson; HAMD= Hamilton rating scale for depression; SSRI - Selective serotonin reuptake inhibitor; TCA= Tricyclic antidepressants; ECT = Electroconvulsive therapy.

to the treatment of people with TRD. Nonetheless, the best way to classify and manage people who relapse during ongoing optimal treatment with antidepressants (that is, who fail to maintain sustained response to treatment) also requires attention and systematic investigation. Most studies of antidepressants are conducted in younger adults and clinicians often have to extrapolate from findings in populations that do not present the same problems as older patients. Older patients often have serious coexisting medical conditions that may contribute to or complicate the treatment of depression. In addition, older adults tend to take multiple medications, some of which may play a role in perpetuating the depressive symptoms. Medical illnesses, concomitant medicine use, functional disability, social isolation, life stressors, bereavement and other losses are more frequent in the elderly and may further complicate their management. The studies reviewed in this paper suggest that being older (Hsieh et al., 2002), living alone, being divorced or separated (Little et al., 1998), having poor physical health (Simpson et

physical health (Simpson et al., 2001), or greater personality morbidity, disability and poor self-rated health (Lenze et al., 2001) are all associated with increased risk of TRD. However, these observational studies fail to provide clinically meaningful information on how best to approach and manage older adults with TRD.

The results of existing meta-analysis of the efficacy of randomised controlled trials (Mittmann et al., 1997; Wilson et al., 2003) suggest that all classes of antidepressants have similar efficacy, although information from head-to-head comparison studies remain sparse. However, recent reports have shown a shift in prescribing antidepressant for the elderly from tricyclic antidepressants to selective serotonin reuptake inhibitors (SSRIs) (Mandani et al., 2000). Expert guidelines have provided further support for such a shift (Alexopoulos et al., 2001), although it remains unclear whether this new approach to the treatment of depression has had any impact on the number of older people with TRD. Weintraub (2001) reported, in a case-series of older adults with TRD, that patients treated with a combination of nortriptyline and a SSRI improved significantly with treatment and remained well for over 1-year afterwards. Several other studies have described a variety of augmentation strategies for the management of TRD, but none were adequately tested in a randomised trial (Amsterdam et al., 1997; Bauer et al., 1998; Charney et al., 1986; Landen et al., 1998; Moreno et al., 1997; Pinto et al., 2002; Price et al., 1990; Rudas et al., 1999). A meta-analysis of placebo-controlled studies including subjects of all ages (that is, not necessarily older adults) concluded that lithium augmentation should be considered as treatment of choice for people who fail to respond to antidepressant therapy (Bauer and Dopfmer, 1999).

The efficacy of ECT for the treatment of TRD has been well documented for young adults, but systematic data on the treatment response of older people remains sparse. Current guidelines suggest that ECT is effective in managing people with TRD (Alexopoulos et al., 2001; Kelly et al., 2000; Prudic et al., 1996) and is superior to SSRI in the treatment of TRD (Folkerts et al., 1997; Tew et al., 1999). At present, there is no systematic information analysing the usefulness of maintenance ECT for the management of older people with TRD.

Conclusion

Treatment resistant depression is relatively common in later life. Mental health professionals working with older adults are becoming increasingly aware of the size of the problem, but clinical practice is still based on relatively loose definitions of TRD and poorly investigated management strategies. It would be suggested that the first necessary step would be the widespread adoption of a set of criteria for the diagnosis of TRD. Secondly, treatment protocols need to be developed and systematic protocols need to be developed and the systematic investigation of factors associated with treatment resistance established for each stage of treatment resistance. This would be a clearly complex task and large randomised multicentre trials will be necessary to establish with some degree of certainty the best way to manage TRD in later life. However difficult such a task might be, we cannot afford not to embrace it.

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