Journal of Affective Disorders 175 (2015) 224–228

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Brief report

Duration of untreated depression influences clinical outcomes and disability

Lucio Ghio [a,*], Simona Gotelli [b], Alice Cervetti [a], Matteo Respino [a], Werner Natta [a], Maurizio Marcenaro [a], Gianluca Serafini [a], Marco Vaggi [b], Mario Amore [a], Martino Belvederi Murri [a]

[a] Department of Neuroscience, Ophthalmology and Genetics, Psychiatry Section, University of Genoa, Italy
[b] Department of Mental Health, ASL3, Genoa, Italy

ARTICLE INFO

Article history:
Received 20 October 2014
Received in revised form
12 January 2015
Accepted 13 January 2015
Available online 21 January 2015

Keywords:
Depression
Untreated illness
Antidepressant
Prevention
Early intervention
Disability

ABSTRACT

Background: The duration of untreated depression (DUD) might have a substantial impact on the clinical outcomes; however, there are important knowledge gaps including the effects on disability and potential differences between first-episode and recurrent episodes of depression.
Methods: We recruited 121 outpatients with first episode and recurrent major depression, and conducted prospective clinical assessments over six months. Clinical outcomes included response to antidepressant therapy, remission and changes in disability.
Results: Patients with a DUD of six months or shorter were more frequently young, unemployed and had higher levels of physical illnesses than those with a longer DUD (all $p < 0.05$). A shorter DUD was associated with significantly higher odds of response at 12 weeks (adjusted odds ratio 2.8; 95% CI: 1.2–6.8) and remission at 24 weeks (4.1; 95% CI: 1.6–10.5) after adjusting for relevant confounders. Changes in disability ratings were analyzed with growth curve analysis and showed steeper declines among those with a shorter DUD. The associations of DUD on clinical outcomes were evident both in patients with first-episode and recurrent depression.
Limitations: Naturalistic design. Self-rated assessment of disability. Findings from subgroup analyses should be replicated in larger sample size.
Conclusions: A shorter duration of untreated depression is associated with more favorable outcomes for major depression, including depression-related disability. This association seems to work both at the first and recurrent episodes, which might have direct implications for both primary and secondary prevention.

1. Introduction

Delivering timely mental health care can influence the long-term outcomes of mental disorders. However, knowledge on this issue is still limited for depression (Ghio et al., 2014).

A seminal study showed that a longer period of time before starting antidepressant drug treatment was associated with a higher probability of persistence of depressive symptoms (Scott et al., 1992). Few studies reexamined this topic (Bukh et al., 2013; de Diego-Adelino et al., 2010; Furukawa et al., 2000; Gormley et al., 1999; Okuda et al., 2010); however, most confirmed the importance of reducing treatment delays. A recent meta-analysis summarized the results from three studies, showing that a shorter duration of untreated depression (DUD) in the first episode was associated with a higher likelihood of response to antidepressant treatment (relative risk of 1.70) and remission from depression (relative risk of 1.65) (Ghio et al., 2014).

However, relevant questions remain regarding the role of the DUD. No study examined whether a shorter DUD is associated with improvements of disability: this would be relevant, given that depression is a major cause of disability worldwide (Ferrari et al., 2013). Also, it is unknown if the DUD impacts clinical outcomes just during the first episode or also later in the illness course (Bukh et al., 2013). In this regard, past research differentiated between the Duration of Untreated Illness (DUI), that is the period between the first episode and the start of treatment, and the Duration of Untreated Episode (DUE), that is between the onset of a recurrent episode and the restart of treatment, without maintenance

Abbreviations: DUD, duration of untreated depression; DUI, Duration of Untreated Illness; DUE, Duration of Untreated Episode; FED, first-episode depression; RED, recurrent episode of depression

* Corresponding author. Tel.: +39 105552978; fax: +39 105556716.
E-mail address: lu.ghio@libero.it (L. Ghio).

http://dx.doi.org/10.1016/j.jad.2015.01.014
0165-0327/

therapy (Ghio et al., 2014). To date, only one study examined the DUI and DUE simultaneously (de Diego-Adelino et al., 2010); the former, but not the latter, was associated with changes in clinical outcomes. However, patients were treated according to a clinical trial protocol, rather than naturalistically, therefore results might be less generalizable to the real-world clinical setting. Given these premises, we planned to assess the effect of the DUD on depression outcomes and disability.

2. Method

2.1. Participants

Eligible patients with a diagnosis of Major Depressive Disorder (MDD) were consecutively recruited from the Outpatient Unit of the Psychiatric Clinic of the University of Genoa and the Voltri Community Mental Health Center during a 12 months period.

Inclusion criteria were a diagnosis of unipolar MDD according to DSM-IV-TR criteria (American Psychiatric Association, 2000), a score of 18 or higher on the 17-item Hamilton depression rating scale (HAM-D) (Hamilton, 1980) and availability to sign an informed consent. We included both participants with first-episode depression (FED) and recurrent episode of depression (RED), that is, with at least one prior episode of depression before the index episode. Patients with RED had to be free from antidepressants since at least 12 months before the current episode. Other reasons for exclusion were other axis I disorders, concurrent psychotherapeutic interventions, pregnancy, lactation, dementia and other intellectual disabilities.

2.2. Procedure

Researchers collected socio-demographic and clinical data, including personal and familiar psychiatric history, previous antidepressant treatment, number of depressive episodes, medical history and number of current physical illnesses. Information on the DUD was collected at baseline using an ad-hoc questionnaire and additional information provided by informants. The DUD for the index episode was defined as the interval between the onset of the current episode and the start of the first adequate treatment, that is the DUI for those with FED and the DUE for those with RED (de Diego-Adeliño et al., 2010).

Patients were treated naturalistically with antidepressant drugs following the recommendations of recent guidelines (NICE, 2010) and were reassessed after 12 and 24 weeks from baseline (± 1 week). Depressive symptomatology was evaluated using the HAM-D. Clinical outcomes were earlier response to treatment, defined as a reduction of at least 50% from the HAM-D-17 baseline score at 12 weeks, and final remission, defined as a score of 7 or less at 24 weeks. Depression-related disability was assessed with the Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002).

2.3. Statistical analyses

Patients were subdivided according to the length of the DUD (≤ 6 months vs. > 6 months) and compared for socio-demographic and clinical features with Chi-square and *T*-tests. Survival analysis was used to estimate differences in the time-to-response and remission from baseline evaluation, using data from 12 and 24 weeks visits. Logistic regression models were conducted to evaluate the effect of DUD on depression outcomes, earlier response and final remission. Lastly, we used multilevel mixed growth curve analysis to examine the changes in disability scores over time nested within individuals (WSAS scores at baseline, 12 and 24 weeks). The linear and quadratic terms of time were tested as fixed parameters, along with the interaction terms with group and other factors (Shek and Ma, 2011). Estimation of the parameters was done using the Restricted Maximum Likelihood Method and Unstructured Covariance model. Analyses were performed using SPSS version 15.0.

3. Results

The sample included 121 patients, treated with SSRIs (71.1%), SNRIs (27.3%) or agomelatine (1.7%). The majority had a DUD of 6 months or shorter ($n=79$, 65%). Table 1 reports the comparison of participants on the basis of the DUD: subjects with a shorter DUD were more frequently younger than 60, unemployed and more frequently physically ill (all $p < 0.05$).

3.1. Effect of DUD on clinical outcomes

Despite receiving less frequent increases of antidepressants dosage, individuals with a shorter DUD showed better outcomes. Subjects with a shorter DUD had higher odds of achieving earlier response (aOR=2.7; 95% CI: 1.1–6.8) and final remission (aOR=5.3; 95% CI: 1.9–14.8), even after adjusting for relevant confounders (see Table 1). In survival analyses on the whole sample, a shorter DUD predicted earlier response (15.2 weeks, 95% CI: 14.7–17.2 vs. 19.4 weeks, 95% CI: 17.6–21.2; log rank $\chi^2=18.4$, df=1, $p < 0.001$) and remission (18.7 weeks, 95% CI: 17.4–20.0 vs. 22.6 weeks, 95% CI: 21.4–23.8; log rank $\chi^2=22.0$, df=1, $p < 0.001$).

3.2. Depression-related disability

Those with a shorter DUD had lower WSAS scores at 12 and 24 weeks (see Table 1 and Fig. 1). In the growth curve model, disability was explained by a negative effect of time ($p=0.003$), by the interaction of DUD with time ($p=0.03$) and positively by the interaction of DUD with the quadratic term of time ($p=0.03$). This indicates that a shorter DUD was associated with more pronounced decreases of disability, with a steeper decline between baseline and 12 weeks than between 12 and 24 weeks. Gender, older age, unemployment, presence of previous episodes of depression and physical illnesses, type of antidepressant did not have significant effects on the course of disability. Instead, antidepressant dosage increase was associated with higher levels of disability at baseline ($p=0.03$) and with a slower decline of disability ($p=0.03$). The model including the DUD had higher fitness than those using only time as a predictor (2LL decrease=145; df=25; $p < 0.001$) or using all predictors except for the DUD (2LL decrease=21; df=3; $p < 0.001$). Changes in WSAS and HAM-D scores from baseline to 24 weeks correlated significantly ($r=0.66$, $p < 0.001$).

3.3. Effect of first vs. recurrent episode of depression

Being in the first episode of depression was associated with higher odds of earlier response (aOR=2.4, 95% CI: 1.1–5.5, $p=0.03$) but not of final remission (aOR=1.9, 95% CI: 0.8–4.7, $p=0.16$). Therefore, we performed exploratory analyses subdividing the sample on the basis of antecedents of depression (FED vs. RED).

Among FED ($n=57$), 41 subjects had a shorter DUD (72%). A shorter DUD was associated with higher odds of earlier response at trend level (aOR=4.0, 95% CI: 0.97–16.0, $p=0.06$), and with final remission (aOR=6.2, 95% CI: 1.5–26.2, $p=0.01$) after adjusting for relevant confounders. Also, a shorter DUD was associated with steeper decreases of WSAS scores at trend level (time *x* group effect $p=0.056$).

Table 1
Clinical and demographic characteristics of the total sample ($n=121$).

	DUD > 6 months ($N=42$)	DUD 0–6 months ($N=79$)	Statistics
Baseline charactheristics			
Age, mean ± SD	56.8 ± 11.2	54.1 ± 10.5	$t=1.29$, df=119, $p=0.19$
Age ≥ 60, %	40.5	22.8	$\chi^2=4.18$, df=1, $p=0.04$*
Genere, *F*, %	71.4	77.2	$\chi^2=0.49$, df=1, $p=0.48$
Education, less than 8 years, %	33.3	36.7	$\chi^2=0.14$, df=1, $p=0.71$
Employed, %	92.9	71.8	$\chi^2=7.34$, df=1, $p=0.007$*
In a relationship, %	57.1	68.4	$\chi^2=1.51$, df=1, $p=0.22$
Living alone, %	26.2	21.8	$\chi^2=0.30$, df=1, $p=0.59$
1 or more physical illnesses, %	35.7	57.0	$\chi^2=4.95$, df=1, $p=0.03$*
Familiarity for psychiatric disorders, %	56.1	53.2	$\chi^2=0.09$, df=1, $p=0.77$
First episode of depression, %	38.1	51.9	$\chi^2=2.10$, df=1, $p=0.15$
previous treatment with AD, %	29.3	33.8	$\chi^2=0.25$, df=1, $p=0.62$
HAM-D baseline, mean ± SD	25.2 ± 4.5	24.0 ± 4.0	$t=1.14$, df=119, $p=0.15$
HAM-D 24 weeks, mean ± SD	10.7 ± 7.8	4.4 ± 4.9	$t=5.39$, df=119, $p<0.001$*
WSAS baseline, mean ± SD	24.3 ± 5.9	22.7 ± 5.2	$t=1.61$, df=119, $p=0.11$
WSAS 24 weeks, mean ± SD	6.2 ± 6.0	11.4 ± 8.2	$t=3.64$, df=119, $p=0.001$*
Treatment and outcomes, %			
SSRI	64.3	77.2	$\chi^2=2.31$, df=1, $p=0.13$
Increase in AD dosage at 12 weeks	35.7	17.7	$\chi^2=4.87$, df=1, $p=0.03$*
Antidepressant switch	38.1	12.7	$\chi^2=10.52$, df=1, $p=0.002$*
Response 12 weeks	38.1	67.1	$\chi^2=9.41$, df=1, $p=0.002$*
Remission 24 weeks	38.1	77.2	$\chi^2=18.1$, df=1, $p<0.001$*
		aOR (95% CI)	Model
Earlier response [a]	ref.	2.7 (1.1–6.8)*	$\chi^2=22.9$, df=9 $p=0.006$*
Final remission [a]	ref.	5.3 (1.9–14.8)*	$\chi^2=36.4$, df=9, $p<0.001$*

DUD, duration of untreated depression; AD, antidepressant drugs; ref., reference category.

[a] Adjusted for gender, older age, presence of physical illness, employment status, baseline HAM-D scores, first vs. recurrent episode, antidepressant switch, antidepressant potentiation/combination.

* $p<0.05$.

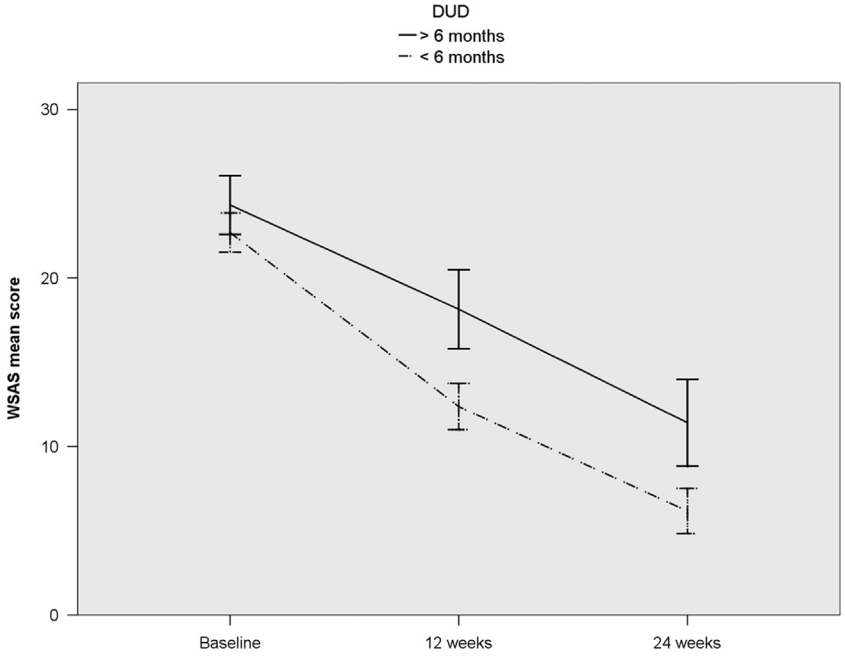

Fig. 1. Changes of depression-related disability (WSAS scores) along follow up. Lines represent unadjusted mean WSAS scores for participants with DUD shorter than 6 months vs. longer than 6 months, error bars represent 95% CI.

Among RED ($n=64$), 38 subjects had a shorter DUD (59.4%). A shorter DUD was not associated with earlier response (aOR=1.7, 95% CI: 0.5–5.6, $p=0.42$), but with final remission (aOR=4.3, 95% CI: 1.3–15.0, p=0.02) after adjusting for relevant confounders. A shorter DUD was also associated with steeper decreases of disability (time *x* group effect $p=0.02$).

4. Discussion

We found that patients with a shorter duration of untreated depression had better clinical outcomes, both in terms of recovery from the symptoms of depression and steeper reductions of depression-related disability. Those receiving antidepressant drugs more timely displayed greater improvements of depressive symptoms and related disability, meaning better recovery of work, home management, social and leisure activities (Mundt et al., 2002). This is consistent with, and extends previous findings (Ghio et al., 2014). Participants with a shorter DUD were more frequently younger, unemployed and physically ill: this might have led to a better recognition of depression (Cepoiu et al., 2008; Menchetti et al., 2009), and to earlier treatment, thus shortening the DUD. However it is unlikely these factors were entirely responsible for the effect of the DUD on clinical outcomes since they were accounted for in the analyses and, except younger age, they impact negatively on antidepressant response and disability (Bagby et al., 2002; Daly et al., 2010). Changes in disability were largely, albeit not entirely, explained by changes in depressive symptoms.

A shorter DUD was linked with better outcomes not just among patients at their first episode of illness but also among those with recurrent episodes, although with less strength. This is in line with other studies that found a significant, linear effects of the DUE on time-to-remission during 12-months follow up (Gormley et al., 1999; Scott et al., 1992). Instead, another recent report failed to detect such an effect, possibly because both the length of follow up period and of the cut-off of the DUE were too short (6 and 8 weeks, respectively) (de Diego-Adelino et al., 2010). Although few studies provide separate data for recurrent episodes (Ghio et al., 2014), linear relationships can be hypothesized between the length of the DUE and clinical outcomes.

These findings support the importance of reducing treatment delays during recurrent depressive episodes as well as during the first. Future studies should clarify which mechanisms underlie the association between a shorter DUD and better clinical outcomes. Intuitively, earlier treatment might better counteract neurobiological changes that occur progressively over the course of depression and tend to self-maintain (Naismith et al., 2012), an example of which would be HPA axis dysregulation (Belvederi Murri et al., 2014). Conversely, other non-biological factors might explain individual delays in seeking treatment and worse outcomes, including maladaptative coping styles, social stigma and personality traits (Bukh et al., 2013).

Our results need to be interpreted in the light of the study strengths and limitations. Patients were representative of the real clinical world. Unlike other studies, we adopted a prospective design, and for the first time assessed disability (Ghio et al., 2014). However, the sample size was small, therefore subgroup analyses should be regarded as hypothesis-generating. Second, diagnoses were not made according to a standardized diagnostic interview and the assessment of disability was self-rated. However, the WSAS has good reliability with clinician-rated outcomes (Mundt et al., 2002). Third, we did not assess compliance to antidepressants systematically, and this might be associated with psychological factors that segregate with a longer DUD. However, frequent contact with GPs was made to monitor prescriptions. Fourth, the study was based on naturalistic design; therefore confounding factors cannot be completely accounted for. Still, results were significant after controlling for several variables that are known to influence the course of depression.

In conclusion, this study showed that a shorter duration of untreated depression is associated with favorable outcomes for major depression, including depression-related disability. This association seems to work both at the first and recurrent episodes: findings might have direct implications for both primary and secondary prevention, similarly to studies on the role of untreated psychosis (Hill et al., 2012; McGorry, 2000) which prompted the implementation of services for early intervention (Ghio et al., 2012; McGorry, 2012). The time might be ripe for evaluating this approach also for major depression, considering its high prevalence and societal costs (Ferrannini et al., 2014).

Role of funding source
None.

Conflict of interest
None.

Acknowledgments
LG and MBM contributed equally to the study conception and design, and to the drafting of the report. MBM and MR conducted the statistical analyses. SG, AC and LG recruited patients and carried out clinical evaluations. WN, MM, GS, MV and MA contributed to the drafting of the article and the interpretation of results.

References

American Psychiatric Association, 2000. Diagnostic and statistical manual of mental disorders DSM-IV-TR. American Psychiatric Association, Washington, DC.
Bagby, R.M., Ryder, A.G., Cristi, C., 2002. Psychosocial and clinical predictors of response to pharmacotherapy for depression. J. Psychiatry Neurosci. 27 (4), 250–257.
Belvederi Murri, M., Pariante, C., Mondelli, V., Masotti, M., Atti, A.R., Mellacqua, Z., Antonioli, M., Ghio, L., Menchetti, M., Zanetidou, S., Innamorati, M., Amore, M., 2014. HPA axis and aging in depression: systematic review and meta-analysis. Psychoneuroendocrinology 41, 46–62.
Bukh, J.D., Bock, C., Vinberg, M., Kessing, L.V., 2013. The effect of prolonged duration of untreated depression on antidepressant treatment outcome. J. Affect. Disord. 145 (1), 42–48.
Cepoiu, M., McCusker, J., Cole, M.G., Sewitch, M., Belzile, E., Ciampi, A., 2008. Recognition of depression by non-psychiatric physicians—a systematic literature review and meta-analysis. J. Gen. Intern. Med. 23 (1), 25–36.
Daly, E.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Gaynes, B.N., Warden, D., Morris, D.W., Luther, J.F., Farabaugh, A., Cook, I., Rush, A.J., 2010. Health-related quality of life in depression: a STAR*D report. Ann. Clin. Psychiatry 22 (1), 43–55.
de Diego-Adelino, J., Portella, M.J., Puigdemont, D., Perez-Egea, R., Alvarez, E., Perez, V., 2010. A short duration of untreated illness (DUI) improves response outcomes in first-depressive episodes. J Affect. Disord. 120 (1–3), 221–225.
Ferrannini, L., Ghio, L., Gibertoni, D., Lora, A., Tibaldi, G., Neri, G., Piazza, A., 2014. Thirty-five years of community psychiatry in Italy. J. Nerv. Ment. Dis. 202 (6), 432–439.
Ferrari, A.J., Charlson, F.J., Norman, R.E., Patten, S.B., Freedman, G., Murray, C.J., Vos, T., Whiteford, H.A., 2013. Burden of depressive disorders by country, sex, age, and year: findings from the global burden of disease study 2010. PLoS Med. 10 (11), e1001547.
Furukawa, T.A., Kitamura, T., Takahashi, K., 2000. Time to recovery of an inception cohort with hitherto untreated unipolar major depressive episodes. Br. J. Psychiatry 177, 331–335.
Ghio, L., Gotelli, S., Marcenaro, M., Amore, M., Natta, W., 2014. Duration of untreated illness and outcomes in unipolar depression: a systematic review and meta-analysis. J. Affect. Disord. 152–154, 45–51.
Ghio, L., Natta, W., Peruzzo, L., Gotelli, S., Tibaldi, G., Ferrannini, L., 2012. Process of implementation and development of early psychosis clinical services in Italy: a survey. Early Interv. Psychiatry 6 (3), 341–346.
Gormley, N., O'Leary, D., Costello, F., 1999. First admissions for depression: is the 'no-treatment interval' a critical predictor of time to remission? J Affect. Disord. 54 (1–2), 49–54.
Hamilton, M., 1980. Rating depressive patients. J. Clin. Psychiatry 41 (12 Pt 2), 21–24.
Hill, M., Crumlish, N., Clarke, M., Whitty, P., Owens, E., Renwick, L., Browne, S., Macklin, E.A., Kinsella, A., Larkin, C., Waddington, J.L., O'Callaghan, E., 2012. Prospective relationship of duration of untreated psychosis to psychopathology and functional outcome over 12 years. Schizophr. Res. 141 (2–3), 215–221.
McGorry, P.D., 2000. Evaluating the importance of reducing the duration of untreated psychosis. Aust. N. Z J. Psychiatry34 (Suppl.), S145S149.
McGorry, P.D., 2012. Truth and reality in early intervention. Aust. N. Z. J. Psychiatry 46 (4), 313–316.
Menchetti, M., Belvederi, M.M., Bertakis, K., Bortolotti, B., Berardi, D., 2009. Recognition and treatment of depression in primary care: effect of patients' presentation and frequency of consultation. J. Psychosom. Res. 66 (4), 335–341.
Mundt, J.C., Marks, I.M., Shear, M.K., Greist, J.H., 2002. The Work and Social Adjustment Scale: a simple measure of impairment in functioning. Br. J. Psychiatry 180, 461–464.

Naismith, S.L., Norrie, L.M., Mowszowski, L., Hickie, I.B., 2012. The neurobiology of depression in later-life: clinical, neuropsychological, neuroimaging and pathophysiological features. Prog. Neurobiol. 98 (1), 99–143.

NICE, 2010. Depression: The Treatment and Management of Depression in Adults (Update). The British Psychological Society and The Royal College of Psychiatrists.

Okuda, A., Suzuki, T., Kishi, T., Yamanouchi, Y., Umeda, K., Haitoh, H., Hashimoto, S., Ozaki, N., Iwata, N., 2010. Duration of untreated illness and antidepressant fluvoxamine response in major depressive disorder. Psychiatry Clin. Neurosci. 64 (3), 268–273.

Scott, J., Eccleston, D., Boys, R., 1992. Can we predict the persistence of depression? Br. J. Psychiatry 161, 633–637.

Shek, D.T., Ma, C.M., 2011. Longitudinal data analyses using linear mixed models in SPSS: concepts, procedures and illustrations. Sci.World J. 11, 42–76.