### REVIEW

**Duration of illness and duration of untreated illness in relation to drug response in psychiatric disorders**

Alfredo Carlo Altamura¹, Massimiliano Buoli†¹ & Marta Serati¹

**Practice points**

- Duration of illness (DI) and duration of untreated illness (DUI) are predictors of poor outcome in the different psychiatric disorders.
- A prolonged DI and DUI are associated with brain abnormalities particularly in schizophrenia.
- Brain abnormalities can play an important role in determining poor treatment response in patients with long DI and DUI.
- DI/DUI has to be taken into account for explaining differences in the efficacy of second-generation antipsychotics in schizophrenics.
- A long DI/DUI is probably associated with less sensitivity to pharmacological treatments and, in particular, to second-generation antipsychotics.

**SUMMARY** Recent literature considers duration of illness (DI) and duration of untreated illness (DUI) as important factors influencing outcome in many psychiatric conditions. The aim of the present article is to analyze the relationship between DI and DUI, and pharmacological response in the different psychiatric disorders with particular emphasis on neurodegenerative aspects. An updated review of the current literature was conducted through PubMed in order to compare different studies focused on DI and DUI, and treatment response in major psychoses and in depressive/anxiety disorders. A significant body of evidence shows that a prolonged DI and DUI is associated with brain abnormalities and poor treatment response, particularly in schizophrenia. Nevertheless, an increasing number of studies point toward a similar conclusion in mood and anxiety disorders as well, even though fewer studies have been published in this field. Given the relationship between a longer DI and DUI, and poor treatment response – not only in schizophrenia but also in mood and anxiety disorders – specific intervention programs aimed to reduce the latency to treatment are definitely envisaged.

Several studies indicate duration of illness (DI) and duration of untreated illness (DUI) as important variables predicting outcome in psychiatric disorders and, in particular, in psychotic ones [1]. Duration of untreated illness, defined as the interval between the onset of a psychiatric disorder according to the current classifications and the administration of the first pharmacological...
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Brain areas negatively associated with DI/DUI across the different psychiatric conditions are summarized in Tables 1 & 2.

Schizophrenia

Brain changes are associated with a long DI as demonstrated by numerous MRI studies. These brain changes appear particularly severe in the first years of illness, being similar to normal aging in late life [9]. Premkumar and colleagues suggest that the right middle frontal cortex is particularly vulnerable to the long-term effect of schizophrenic illness, whereas the dorsomedial prefrontal cortex, fusiform gyrus and cerebellum are affected by both a long DI and aging [10]. Another MRI study by the same group showed that there was a significant exponential relation between the DI and the volumes of prefrontal cortex, parieto-occipital cortex gray matter, thalamus and putamen, suggesting that these regions are susceptible to change if the disorder persists [11]. DI has been negatively associated with gray matter volume in prefrontal regions bilaterally, in the temporal pole on the left and the caudal superior temporal gyrus on the right [12]. In a 5-year MRI longitudinal study with 96 schizophrenic patients the progression...
in left frontal density loss appeared to be related to an increased number of psychotic episodes, with atypical antipsychotics attenuating these changes [13]. The loss of prefrontal gray matter volume is confirmed by other previous studies [14]. Bilateral insular cortex volumes have been negatively correlated with DI [15]. No differences were found in thalamic volume between first-episode versus chronic schizophrenic patients [16].

An association between prolonged DUI/DUP and decreased temporal volume has been reported [17]. This observation was confirmed in a MRI trial in which a loss of the left planum temporal gray matter was associated with a long DUP, suggesting a role of this specific area in the initial phases of untreated psychosis [18]. Bangalore and colleagues investigated the effect of DUI on brain structures in minimally treated psychotic patients by MRI, finding that DUI inversely correlated with gray matter (i.e., the longer the DUI, the lower the gray matter density) of the left fusiform gyrus, left lingual gyrus, left declive and right parahippocampal gyrus [19]. Such results are consistent with the observations of a recent study reporting decreased gray matter in the left middle and inferior temporal, left occipital and left fusiform cortices [20]. Hippocampal volumes seem not to be altered by a long DUP [21], even though a very recent study reported that the length of DUP associated positively with reduced densities of the right limbic area and the right hippocampus [22].

Finally, a minority of dated studies failed to find a relationship between length of DUP and brain changes in schizophrenic patients [23, 24].

Table 1. Brain areas involved in patients with long duration of illness.

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Brain areas</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Schizophrenia</td>
<td>Right middle frontal cortex</td>
<td>[10]</td>
</tr>
<tr>
<td></td>
<td>Dorsomedial prefrontal cortex</td>
<td>[10]</td>
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<tr>
<td></td>
<td>Fusiform gyrus</td>
<td>[10]</td>
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<tr>
<td></td>
<td>Cerebellum</td>
<td>[10]</td>
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<tr>
<td></td>
<td>Parieto-occipital cortex</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>Thalamus</td>
<td>[11]</td>
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<tr>
<td></td>
<td>Putamen</td>
<td>[11]</td>
</tr>
<tr>
<td></td>
<td>Temporal pole</td>
<td>[12]</td>
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<tr>
<td></td>
<td>Caudal superior temporal gyrus</td>
<td>[12]</td>
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<tr>
<td></td>
<td>Insular cortex</td>
<td>[19]</td>
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<tr>
<td>Bipolar disorder</td>
<td>Hippocampus</td>
<td>[27, 28]</td>
</tr>
<tr>
<td></td>
<td>Cerebellum</td>
<td>[27]</td>
</tr>
<tr>
<td></td>
<td>Fusiform cortex</td>
<td>[27]</td>
</tr>
<tr>
<td></td>
<td>Left middle frontal cortex</td>
<td>[29]</td>
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<tr>
<td></td>
<td>Dorsolateral prefrontal cortex</td>
<td>[31]</td>
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<td>Major depressive disorder</td>
<td>Hippocampus</td>
<td>[35]</td>
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<tr>
<td></td>
<td>Subcallosal gyrus</td>
<td>[38]</td>
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<tr>
<td>Panic disorder</td>
<td>Left putamen</td>
<td>[40]</td>
</tr>
<tr>
<td>Obsessive–compulsive disorder</td>
<td>Hippocampus</td>
<td>[41]</td>
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<tr>
<td></td>
<td>Amygdala</td>
<td>[41]</td>
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### Bipolar disorder

Evidence of neurodegeneration in bipolar patients with a long DI is less robust compared with schizophrenic ones. A 4-year follow-up MRI study showed a greater gray matter loss in the hippocampus, cerebellum and fusiform cortex in 20 bipolar patients compared with healthy controls [27]. Other authors reported a loss of hippocampal volume in bipolar patients with a long DI [28]. DI in bipolar subjects has been inversely correlated with the cortical thickness of the left middle frontal cortex [29]. Lateral ventricles seem to be larger in multiple-episode bipolar patients compared with first-episode ones [30]. In particular manic episodes, but not major depressive episodes, would be associated with a gray matter reduction in dorsolateral prefrontal cortices [31]. On the other hand, other authors reported that the number of previous major mood episodes and DI were not significantly correlated with gray and white matter volume in bipolar disorder [32, 33]. Finally, no correlations were found between DUI and white matter hyperintensities, a neuroimaging abnormality typical of bipolar disorder [34].

As mentioned earlier, brain neurodegenerative processes in bipolar patients seem to be less extensive than in schizophrenics and, being manic episodes, probably more ‘toxic’ than major depressive ones; studies comparing bipolar I and II are warranted to detect eventual differences in these two subgroups of patients.
Table 2. Brain areas involved in patients with long duration of untreated illness.

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Brain area</th>
<th>Ref.</th>
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<tbody>
<tr>
<td>Schizophrenia</td>
<td>Left planum temporal</td>
<td>[18]</td>
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<td></td>
<td>Left fusiform gyrus</td>
<td>[19]</td>
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<td></td>
<td>Left lingual gyrus</td>
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<td>Left declive (cerebellum)</td>
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<td></td>
<td>Right parahippocampal gyrus</td>
<td>[19]</td>
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<td></td>
<td>Left middle temporal cortex</td>
<td>[20]</td>
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<td></td>
<td>Inferior temporal cortex</td>
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<td></td>
<td>Left occipital cortex</td>
<td>[20]</td>
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<tr>
<td></td>
<td>Hippocampus</td>
<td>[22]</td>
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<tr>
<td>Bipolar disorder, major depressive disorder and anxiety disorders</td>
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<td>–</td>
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</table>

**DI/DUI & treatment response**

**Schizophrenia**

Treatment response to antipsychotics has been negatively correlated with DI and DUI/DUP in schizophrenia. In a recent study, DI was found to be predictive of treatment response to olanzapine and risperidone during acute episodes of schizophrenia [44]. Similar results were found regarding electroconvulsive therapy: long DI would portend poor response to electroconvulsive therapy in 253 patients with treatment-resistant schizophrenia [45].

A longer DUP was associated with greater morbidity in the early course of schizophrenia: a systematic meta-analysis of 43 studies investigating the relationship between DUP and outcome in first-episode schizophrenia found that a prolonged DUP was associated with poor response to pharmacological treatment and no symptomatic/functional recovery [46]. A previous study by the same group found that a shorter DUP was associated with better clinical response, including improvement in overall psychopathology and negative symptoms. Furthermore, a longer DUP was found to predict more severe positive and negative symptoms and poorer social function at 1 year in 98 patients with first-episode schizophrenia [47]. The impact of the DUP prior to first psychiatric admission on the 15-year outcome in schizophrenia was analyzed by Bottlender and collaborators in 2003 [48]. They found that a longer DUP was associated with more pronounced negative, positive and general psychopathological symptoms as well as a lower global functioning 15 years after the first psychiatric admission. These data are confirmed by previous retrospective studies [49,50].

Of clinical interest, the relationship between DUP and outcome has been analyzed prospectively in different follow-up periods. An 8-year prospective naturalistic study by Harris [51] involving 318 first-episode psychotic patients found that a shorter DUP (≤3 months) correlated moderately with a better treatment response on positive symptoms and with a better social functioning and quality of life in comparison with a longer DUP (>3 months). Other studies confirmed the relation between a long DUP and a scarce pharmacological response on negative symptoms [5], as well on cognitive symptoms [47,52–55]. It has been reported that short DUP, associated with greater response to antipsychotic treatment, may underlie a subgroup with better prognosis; furthermore, a meta-analysis conducted by
Marshall and coworkers showed that patients with a long DUP were significantly less likely to achieve remission [56]. Haas and coworkers in 1998 examined the effect of DUP and DI on treatment response and the relation between these two variables [50]. Interestingly patients with a DUP of more than 1 year showed a worse response to pharmacological treatment during hospitalization compared with patients with a short DUP independently of the DI.

The length of DUP seems to be strongly associated with poor pharmacological response in schizophrenics. By contrast, a negative effect of DI on treatment response of schizophrenics is shown only by two very recent studies [44,45] and these preliminary data have to be confirmed by further studies.

**Bipolar disorder**

A recent trial found that the number of previous major affective episodes but not DUI was associated with lithium response in 100 bipolar patients [57]. A similar correlation between number of major affective episodes and lithium response with no effect of DI was found in 179 manic bipolar patients [58]. By contrast, in a sample of 35 resistant bipolar patients, treatment response to gabapentin was correlated with DI [59]. A previous trial found a significant correlation between DI and response to quetiapine in 145 psychotic patients (bipolar and schizophrenic) [60]. Finally, the results from a naturalistic study conducted by our group demonstrated that a longer DUP was associated with a higher number of suicide attempts and attempters in a sample of 320 bipolar patients [61].

In contrast to schizophrenia, DI but not DUI seems to be associated with poor treatment response in bipolar disorder. The data, however, are preliminary and further research is necessary.

**Major depressive disorder & anxiety disorders**

More data associated with bipolar disorder indicate DI and DUI as negatively correlated with treatment response in major depressed patients. Preliminary results indicated that patients with a DI of more than 2 years were less likely to respond to antidepressant and electroconvulsive therapy treatment in comparison with patients with a DI of up to 2 years [62]. In a recent trial, treatment response to escitalopram was found to be associated with a DI of less than 1 year in a sample of 2050 depressed elderly patients [63].

In a sample of 13 outpatients a correlation between DUI and treatment response/remission to fluvoxamine was found [64]. A total of 141 major depressed patients with a shorter duration of untreated episode showed a faster response to antidepressant treatment in comparison with patients presenting a longer duration of untreated episode [65]. In a trial conducted by our group, 68 patients affected by major depressive disorder and with a DUI of more than 1 year exhibited a higher number of recurrences under antidepressants compared with patients with a DUI of less than 2 years, indicating a poor response to long-term treatment [66].

Regarding anxiety disorders, preliminary data indicate a positive association between the length of DUI/DI and treatment response. In a naturalistic trial, 49 patients affected by panic disorder and with a long DI achieved treatment response with higher doses of imipramine in comparison with patients with a short DI [67]. In a trial conducted by our group, 96 patients affected by panic disorder had a higher probability of developing a subsequent major depressive disorder when presenting with a DUI of more than 1 year [68]. Data from three placebo-controlled multicenter trials showed that DI was a predictor of treatment response in patients affected by social anxiety disorder [69]. By contrast, in a more recent publication, a correlation between DI and treatment response in social phobia was not found [70]. A preliminary report indicated that response to venlafaxine was associated with a short DI in 32 patients with generalized anxiety disorder [71]. In another study, 100 patients with generalized anxiety disorder and a long DUI showed a more complicated course of illness, with high rates of comorbid psychiatric disorders with onset later than generalized anxiety disorder [72]. In two multicenter double-blind studies, treatment response to clomipramine in obsessive–compulsive patients was associated with a short DI [73]. These findings were confirmed by others [74]. Moreover, short DI predicted early response to antidepressants in OCD patients [75]. More recently it has been shown that a DUI of up to 24 months was predictive of treatment response in 66 OCD patients [76].

Major depressive and OCD patients seem to be less responsive to pharmacological treatment when showing a long DI/DUI. Preliminary data show similar results for DI and treatment response in patients affected by panic disorder, generalized anxiety disorder and social phobia.
No studies have investigated the relationship between DI/DUI and treatment response in post-traumatic stress disorder.

**Conclusion**

The majority of available data seem to show that a longer DI or DUI is associated with a reduced response to treatment in the different psychiatric disorders and, in the case of schizophrenia, to a worse outcome. The negative role of DI/DUI seems well established in schizophrenia, while data on mood and anxiety disorders should be considered as preliminary. In the case of bipolar disorder, for example, the number of major mood episodes instead of DI/DUI seems to be more relevant for predicting outcome of this clinical condition. The importance of these clinical variables on outcome of psychiatric disorders opens three interesting issues: the first is on the potential biological (and cognitive) factors responsible for the ‘toxic’ effect of DI/DUI; the second is represented by the clinical strategies to prevent a long DI/DUI [1]; and finally the third consists of the role of these variables in predicting outcome with possible implications on the treatment strategies of the nosographic guidelines.

The choice to review literature about DI/DUI across such a broad spectrum of psychiatric disorders is due to the importance of this clinical variable to predict outcome independently of the diagnosis. If the preliminary studies were focused on schizophrenia, recent literature would indicate DI/DUI as an important prognostic factor also for mood and anxiety disorders. The exact knowledge of the available data for DI/DUI, not only in schizophrenia, but also in mood and anxiety disorders, can help the clinician in the selection of the best treatment for patients.

Given that the relationship between a longer DUI and a worse outcome has been particularly stressed in the field of schizophrenia and first-episode psychosis, it is not surprising that the majority of interventions aim to reduce the latency to treatments in this specific area of mental disorders. Basically, early intervention has two main objectives: the first is to prevent the onset of schizophrenia in people with prodromal symptoms; and the second is to provide effective treatment to schizophrenics in the early stages of the illness, with the goal of reducing the severity of the illness [77].

Duration of untreated illness/DI have to be taken into account when explaining the discrepancy in efficacy of second-generation antipsychotics in schizophrenics. It is clear that, given the neurodegenerative process, patients with a longer DI/DUI show less sensitivity to the pharmacological activity of second-generation antipsychotics in comparison with patients with a shorter DI/DUI. Therefore, differences in the efficacy of second-generation antipsychotics versus neuroleptics are more difficult to detect in populations with long DI/DUI, where drug resistance associated with neurodegeneration is more likely [78].

In the field of affective disorders there has been great attention in terms of prevention programs in different populations. In particular, prevention programs subdivided into universal prevention, selective prevention and indicated prevention according to the presence of risk factors/soft symptoms, and basically represented by educational and psychological treatments, have been reviewed and grouped in meta-analyses with small but significant effect sizes, particularly in the short term [79–81].

Primary and secondary prevention are the only strategy that clinicians can use to prevent the brain damage related to a long DI/DUI. Future research has two main objectives: first, biological factors underlying the negative effects of DI/DUI on brain integrity have to be well investigated and established. Second, the role of pharmacotherapy on blocking neurodegeneration across psychiatric disorders has to be better defined. Preliminary data indicate that both antidepressants [82] and atypical antipsychotics [13] have a beneficial effect in preventing neurodegeneration correlated with a long DI/DUI. However, the effect size and differences between molecules in protecting patients from neurodegeneration still have to be established.

It is too early to envisage introduction of these variables in nosography (e.g., DSM-IV-TR or International Classification of Diseases) as specific predictors for outcome or for managing treatment strategies of evidence-based therapeutic guidelines. However, this article aims to stress this potentiality should be considered and research on these domains are mandatory to prevent or reduce drug resistance and ameliorate outcome in the different psychiatric disorders [83].

Finally, some limits of the studies mentioned in the present article have to be described. First, the studies investigating the relationship between DI and treatment response have the bias not to take into account the effects of previous
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**Future perspective**
Future research has the objective to investigate the reasons why DI/DUI have such a negative role on treatment response and outcome in different psychiatric conditions. DI/DUI are probably the clinical ‘epiphénomene’ of common pathogenic factors among the different psychiatric disorders. Different hypotheses have been formulated about this issue. Neurodegenerative aspects certainly have an important role in explaining the poor treatment response in patients with DI/DUI as demonstrated by studies mentioned earlier. An alternative hypothesis is that patients with a long DUI/DI represent a subgroup with scarce insight and a more severe psychopathology that would justify a poorer response to pharmacological treatments. Finally, patients with a long DI/DUI could be genetically predisposed to chronicity or a more severe psychopathology with a delay of an adequate pharmacological treatment. Further neuroimaging, genetic and clinical studies will clarify the pathogenetic factors underlying DI/DUI and will direct clinicians to the best prevention strategies and treatment options.

**Financial & competing interests disclosure**
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No writing assistance was utilized in the production of this manuscript.

**Bibliography**
Papers of special note have been highlighted as:
- of considerable interest
- of interest

Supports the neurodegenerative model of bipolar disorder.


Duration of illness & duration of untreated illness in relation to drug response in psychiatric disorders


Reviews the factors associated with drug resistance in schizophrenia.


