Impact of Duration of Antidepressant Treatment on the Risk of Occurrence of a New Sequence of Antidepressant Treatment

Authors: H. Verdoux[1,2], A. Cougnard[1,2], A. Thiébaut[3], M. Tournier[1,2]

Affiliations:
[1] Université Bordeaux 2, Bordeaux, France
[2] INSERM U657, Bordeaux, France
[3] INSERM U657, Paris, France

Abstract

Introduction: Despite the recommendation that antidepressant treatment should be continued for several months to reduce the risk of relapse/recurrence of depression, early discontinuation is frequent in naturalistic conditions. The study was aimed at exploring the impact of early discontinuation of antidepressant treatment on the risk of antidepressant re-initiation.

Methods: A follow-up study of persons (n = 35 053) starting antidepressant treatment was performed using a representative sample of the French Social Security Insurance national database.

Results: The risk of re-initiation of antidepressant treatment was higher if the duration of the index episode of antidepressant treatment was ≥ 6 months [hazard ratio (HR) = 2.35; 95 % CI 2.25–2.45) or 2–5 months (HR = 1.65; 95 % CI 1.59–1.71) compared to ≤ 1 month. The other characteristics independently associated with re-initiation of treatment were older age, female gender, low income, serious chronic illness, index prescription by a specialist and co-prescription of other psychotropic drugs.

Conclusions: The lower risk of re-initiation of antidepressant treatment in persons with shorter-than-recommended duration of antidepressant treatment might be explained by over-prescription of antidepressants in persons with sub-threshold symptoms.

received 21.09.2010
revised 14.12.2010
accepted 14.12.2010

Bibliography
DOI http://dx.doi.org/10.1055/s-0031-1271686
Published online ahead of print: 16 February 2011
Pharmacopsychiatry 2011; 44: 96–101

ISSN 0176-3679

Correspondence
Prof. H. Verdoux
Hôpital Charles Perrens
121 rue de la Béchade
33076 Bordeaux Cedex
France
Tel.: +33/556/561 732
Fax: +33/556/563 546
helene.verdoux@u-bordeaux2.fr

Introduction

A cornerstone recommendation in clinical guidelines on antidepressant treatment in major depression is that it should be continued several months after recovery in order to reduce the risk of relapse/recurrence [1–3]. This recommendation is mostly supported by the findings of randomized controlled trials (RCTs) showing that the risk of relapse is dramatically reduced when the antidepressant treatment is continued [4, 5]. In spite of these findings, the recommendation of continuing antidepressant treatment after the remission of depressive symptoms is poorly respected in naturalistic conditions and a large proportion of antidepressant treatments are used for less than the recommended duration [6, 7]. Hence, the prognostic impact of early discontinuation of antidepressant treatment also needs to be explored in real-life conditions.

Controversial findings have been reported by the few observational studies addressing this issue. In the first study by Melfi and colleagues [8] performed on a Medicaid database, duration of treatment was assessed over a 6-month treatment period. Relapse/recurrence was assessed over an 18-month follow-up period after a gap of at least 6 months after the end of antidepressant treatment, and was defined by reinitiation of antidepressant treatment or occurrence of suicide attempt, psychiatric hospitalization or psychiatric emergency visit. This study showed that persons with early discontinuation were more likely to present with a relapse or recurrence over a 2-year follow-up period. Similar findings were obtained by 2 other studies based upon a comparable method carried out respectively on an US insurance database [9] and on an UK primary-care date database [10]. However, in a 5-year follow-up study carried out on a Dutch database including pharmacy dispensing records, Gardarsdottir and colleagues [11] found that persons who continued antidepressant treatment for less than 6 months were at lower risk of reinitiation of antidepressant treatment compared to persistent users. This issue has to be clarified as there is growing concern regarding the benefit/risk ratio of antidepressant drugs [12, 13].

The aim of the present study was to assess in naturalistic conditions the impact of early discontinuation of antidepressant treatment on the risk of antidepressant re-initiation.

Methods

Setting and study design

Data were drawn from the French Social Security Insurance (SSI) national database recording information on drugs refunded to nearly 75% of the French general population [14]. The present study was carried out on a database including a representative sample of 1% of persons insured by the SSI. This sample called *Echantillon Généraliste des Bénéficiaires (EGB)* (for Generalist Sample of SSI Beneficiaries) was implemented in 2004. Due to space and memory constraints, information on health-care consumption of the whole sample of SSI beneficiaries is conserved only for 2 years. The EGB is a cohort of beneficiaries for whom information on health-care consumption is conserved up to 20 years, thereby allowing assessment of their longitudinal pattern of health-care use for economic or research purposes [15]. The randomization criterion is the SS identification number. The identification of persons included in this sample is protected by an anonymization process with 2 cryptographic levels, a procedure conforming to French data protection legislation. The present study was approved by bioethics committees.

The EGB database includes data on community claims for reimbursement of drugs on the market classified using the WHO Anatomical Therapeutic Chemic (ATC) index [16]. The present study was performed on the 2005–2007 EGB database in a cohort of persons aged 18 years and over with a new dispensing of antidepressant in 2005–2006, defined as no dispensing in the 6 months prior to the index dispensing. This 6-month criterion was chosen because comprehensive data collection on health-care consumption was really effective at the beginning of the second semester of 2004, hence the criterion "no dispensing of antidepressant" could be documented only for this period. Patients were followed up until the occurrence of the outcome of interest or the end of the follow-up period (2007, December 31st).

Index episode of antidepressant treatment

No information on either the prescribed dosage or the duration of the prescription is available in the database. Hence, duration of the index episode of antidepressant treatment was estimated using information on dates of antidepressant dispensings. Since dispensings are for a maximum of 28 days, we defined discrete 28-day periods after the index delivery. Over each 28-day period, we postulated that the cumulative duration of antidepressant treatment was 28 days if there was at least one delivery of antidepressant, irrespective of the number of deliveries. Discontinuation of antidepressant treatment was considered to have occurred in the event of non-renewal 56 days after the last delivery (i.e., the 28-day period following a 28-day period with delivery). Duration of the index antidepressant episode was calculated irrespective of the types of antidepressants prescribed, i.e., without taking into account the event of switching from an antidepressant product to another over the episode.

According to the findings of the prior study exploring duration of the index episode of antidepressant treatment [6], we a priori categorized this duration as (i) "ultra-short" i.e., including only one 28-day period (defined hereafter as "≤1 month"); (ii) "short" if the duration was > to 28 days and < to 168 days (defined hereafter as "2–5 months"); (iii) "long" if the duration was ≥168 days (defined hereafter as "≥6 months").

Outcome

The outcome of interest was the occurrence of a second episode of antidepressant treatment, defined as reinitiation of antidepressant treatment after a gap of at least 56 days between 2 deliveries.

Other variables of interest

4 antidepressant classes were defined according to the ATC classification: (i) tricyclic antidepressants; (ii) selective serotonin reuptake inhibitors (SSRIs), (iii) monoamine oxidase inhibitors (MAOIs); (iv) others (mianserine, milnacipran, mirtazapine, tianeptine, viloxazine, venlafaxine).

The EGB database includes data on demographic characteristics: age, gender, and welfare benefit for persons with very low income *(couverture maladie universelle complémentaire, CMU-C)*. Diagnoses or indication for prescribing are not collected in this database. The status "long duration disease" may be used as a proxy for the presence of a serious chronic illness. This status, which gives access to treatment free of charge, is restricted to persons presenting with a chronic and costly disease (e.g., disabling stroke, cancer, psychosis). In the present study, this characteristic was categorized as "no chronic illness" vs. "psychiatric chronic illness" vs. "other chronic illness". A further categorization of "psychiatric chronic illness" was not relevant since only broad diagnostic categories are used in this classification (e.g., "psychosis"), often with little correspondence with international diagnostic categories.

The prescriber of the index antidepressant treatment was categorized as (i) general practitioner (GP); (ii) private psychiatrist; (iii) hospital practitioner (no information is available in the SSI database on the specialty of the prescriber for hospital practitioners); (iv) other private specialists. The other psychotropic drugs delivered during the index episode were categorized as: (i) anxiolytics/hypnotics (benzodiazepines, carbamates and others); (ii) antipsychotics; (iii) mood stabilizers (lithium, sodium divalproate, valpromide, carbamazepine, oxcarbazepine, lamotrigine, topiramate).

Statistical analyses

Analyses were conducted using STATA 9 software [17]. Kaplan-Meier survival curves were constructed to examine time to reinitiation of antidepressant treatment between the 3 groups defined by duration of index episode of antidepressant treatment: (i) "ultra-short" (≤1 month); (ii) "short" (2–5 months); and (iii) "long" (≥6 month). We investigated the impact of the duration of the index episode of antidepressant treatment on the risk of reinitiation of antidepressant treatment using Cox proportional hazards regression models. Duration of follow-up was calculated from the end of the index episode of antidepressant treatment (i.e., 56 days after the last dispensing) to the date of reinitiation of antidepressant, or to the end of the follow-up period. We defined ultra-short duration as our reference category. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Efron approximation to handle events occurring at the same time in different patients (ties) [18].

The model was *a priori* adjusted for the following variables: (i) age categorized into 7 levels (see **Table 2**); (ii) gender; (iii) presence of welfare benefit; (iv) presence of a serious chronic illness; (v) dispensing of other psychotropic drugs over the index episode; (v) type of prescriber. All these variables were found to

be associated to duration of index treatment in a prior study [6] and may also have an impact on the likelihood of reinitiation of antidepressant treatment.

We subsequently explored whether the impact of duration of index episode of antidepressant treatment varied according to the classes of antidepressant by using distinct Cox models including persons treated exclusively by one class of antidepressant during the index episode. Lastly, we performed sensitivity analyses in order to examine whether our gap definition (at least 56 days between 2 deliveries of antidepressant treatment) could have an impact on the findings, for example, by misclassifying delayed deliveries as treatment interruptions. We used 2 other definitions of the gap duration reducing this period to 42 days or increasing it to 70 days (i.e., 56 ± 14 days).

Results

Characteristics of the sample

Of the 479 319 persons included in the EGB database, 35 053 (7.3 %) presented with an incident dispensing of antidepressant in 2005–2006. They had a mean age of 50.2 years (SD 17.6) and 23 473 (67 %) were females. The characteristics of the index episode of antidepressant treatment have been described elsewhere [6]. Briefly, most antidepressant treatments were initiated by a GP (n = 28 585, 81.6 %). More than half of the index episodes were of ultra-short duration (< 1 month, n = 20 377, 58.1 %), a quarter were of short duration (2–5 months, n = 8 297, 23.7 %) and less than 1 out of 5 were of long duration (≥ 6 months, n = 6 379, 18.2 %). The characteristics of the 3 groups defined by the duration of the index episode are presented in **Table 1**.

Risk of reinitiation of antidepressant treatment

Nearly half of the persons (n = 16 855, 48.1 %) presented with a second episode of antidepressant treatment over the follow-up. The proportion of second episodes was higher in the short duration group (2–5 month, n = 4 893, 59 %) compared to the long duration group (≥ 6 months, n = 3 234, 50.7 %) and the ultra-short duration group (< 1 month, n = 8 728, 42.8 %).

The median duration between the index and the second episode was 99 days (interquartile range 50–266). The Kaplan-Meier survival curves for the 3 groups of duration of index episode are presented in **Fig. 1**, showing that persons in the long duration group were the most likely to present with a new episode of antidepressant treatment. The findings of multivariate Cox proportional hazards analyses are reported in **Table 2**. After adjustment for the other characteristics, persons with an index episode of long (≥ 6 months) or short (2–5 months) duration were at increased risk of reinitiation of antidepressant treatment compared to those with ultra-short duration (≤ 1 month). The other characteristics independently associated with increased risk of treatment reinitiation were older age, being a female, receiving welfare benefit, presenting with a serious chronic illness, antidepressant prescription by a psychiatrist or a hospital practitioner and co-prescription of other psychotropic drugs.

We performed further analyses after excluding the persons with ultra-short duration in order to compare persons with short and long duration of antidepressant treatment. The risk of antidepressant reinitiation was significantly higher in persons treated at least 6 months compared to persons treated 2–5 months (adjusted HR = 1.41, 95 % CI 1.34–1.47, 95 % CI p = 0.0001).

Since persons with psychotic or bipolar disorder were excluded from prior studies [8–10, 19], we explored whether the findings were modified after exclusion of persons with antipsychotic or mood stabilizer prescribing during the index episode of antidepressant treatment. The findings of the Cox survival analysis were the same after exclusion of these persons (n = 3 000): short duration vs. ultra-short duration: adjusted HR 1.64 (95 % CI 1.58–1.70, p = 0.0001); long duration vs. ultra-short duration: adjusted HR 2.39 (95 % CI 2.28–2.50, p = 0.0001).

Table 1 Characteristics of patients according to duration of index episode of antidepressant treatment.

	Duration of antidepressant					
	1 month (N = 20 377; 58.1 %)		2–5 months (N = 8 297; 23.7 %)		≥ 6 months (N = 6 379; 18.2 %)	
	Mean	SD	Mean	SD	Mean	SD
age	49.0	17.5	50.5	17.3	53.8	17.8
	N	%	N	%	N	%
male gender	6 893	33.8	2 719	32.8	1 968	30.8
welfare benefit[a]	2 210	10.8	720	8.7	431	6.8
serious chronic illness[b]						
no	15 878	77.9	6 235	75.2	4 262	66.8
psychiatric	567	2.8	357	4.3	430	6.7
other	3 932	19.3	1 705	20.6	1 687	26.5
other psychotropic drugs	11 174	54.8	5 811	70.0	5 249	82.3
anxiolytics/hypnotics[c]	10 611	52.1	5 569	67.1	5 074	79.5
antipsychotics	868	4.3	654	7.9	1 009	15.8
mood stabilizers[d]	242	1.2	195	2.3	322	5.0
antidepressant prescriber						
general practitioner	16 986	83.4	6 680	80.6	4 919	77.2
psychiatrist	758	3.7	490	5.9	485	7.6
hospital practitioner[e]	1 596	7.8	764	9.2	757	11.9
other specialist	1 021	5.0	352	4.3	214	3.4

[a] Benefit for persons with very low income (couverture maladie universelle complémentaire)

[b] "Long duration disease" status giving access to treatment free of charge (see text)

[c] Benzodiazepines, carbamates and others;

[d] Lithium, sodium divalproate, valpromide, carbamazepine, lamotrigine, oxcarbazepine, topiramate

[e] No information is available in the Social Security Insurance database on the speciality of the prescriber for hospital practitioners

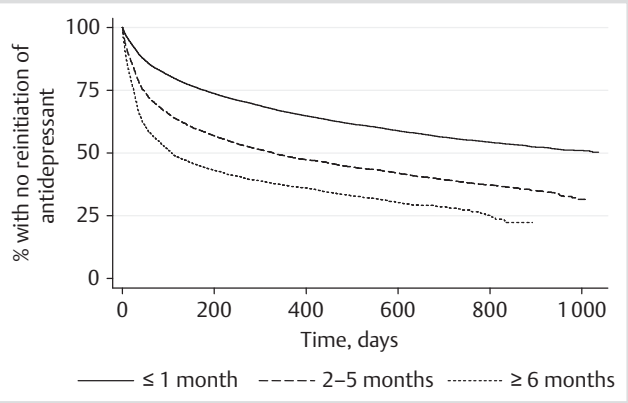

Fig. 1 Kaplan-Maier survival curves showing the proportion of patients with no reinitiation of antidepressant treatment according to duration of index episode.

Table 2 Risk of reinitiation of antidepressant treatment according to duration of index episode: Cox survival multivariate analyses.

	HR[a]	95% CI[b]	p
duration of antidepressant treatment			
– 1 month	1		
– 2–5 months	1.65	1.59–1.71	0.0001
– ≥6 months	2.35	2.25–2.45	0.0001
age (years)			
– 18–24	1		
– 25–34	1.29	1.18–1.41	0.0001
– 35–44	1.45	1.33–1.57	0.0001
– 45–54	1.57	1.44–1.71	0.0001
– 55–64	1.50	1.37–1.64	0.0001
– 65–74	1.57	1.44–1.64	0.0001
– ≥75	1.50	1.37–1.64	0.0001
gender			
– male	0.80	0.76–0.83	0.0001
welfare benefit[c]			
– yes	1.19	1.13–1.25	0.0001
serious chronic illness[d]			
– *no*	1		
– *psychiatric*	1.61	1.50–1.73	0.0001
– *other*	1.12	1.08–1.17	0.0001
other psychotropic drugs[e]			
– yes	1.45	1.11–1.18	0.0001
antidepressant prescriber			
– general practitioner	1		
– psychiatrist	1.20	1.13–1.29	0.0001
– hospital practitioner[f]	1.07	1.02–1.13	0.0001
– other specialist	1.06	0.99–1.15	0.10

[a] Hazard ratio

[b] 95% confidence interval

[c] Benefit for persons with very low income *(couverture maladie universelle complémentaire)*

[d] "Long duration disease" status giving access to treatment free of charge (see text)

[e] Anxiolytics, hypnotics, antipsychotics, mood stabilizers

[f] No information is available in the Social Security Insurance database on the speciality of the prescriber for hospital practitioners

Analyses by antidepressant classes

Regarding the classes of antidepressant, the most frequently prescribed were SSRIs (n = 22 111, 63.1%). followed by "other" antidepressants (n = 10 650, 30.4% including mostly venlafaxine, tianeptine and mianserine), tricyclics (n = 5 252, 15.0%) and MAOIs (n = 136, 0.4%). Most patients were prescribed a single class of antidepressant over the index episode (n = 32 172, 91.8%). The findings of the Cox survival analyses were similar irrespective of the antidepressant class: that is, short and long duration were always associated with an increased risk of antidepressant reinitiation compared to ultra-short duration: 1) SSRIs: short duration vs. ultra-short duration: adjusted HR 1.63 (95% CI 1.55–1.70, p = 0.0001); long duration vs. ultra-short duration: adjusted HR 2.25 (95% CI 2.13–2.38, p = 0.0001); 2) "other" antidepressants: short duration vs. ultra-short duration: adjusted HR 1.55 (95% CI 1.45–1.67, p = 0.0001); long duration vs. ultra-short duration: adjusted HR 2.26 (95% CI 2.07–2.48, p = 0.0001); 3) tricyclics: short duration vs. ultra-short duration: adjusted HR 3.27 (95% CI 2.74–3.90, p = 0.0001); long duration vs. ultra-short duration: adjusted HR 1.34 (95% CI 1.0–1.82, p = 0.05). Separate analyses were not performed for MAOIs owing to the small number of persons included in this group.

Sensitivity analyses

Sensitivity analyses based upon other definitions of duration of treatment interruption defining a new episode (gap) showed similar findings: (i) 42 days instead of 56 days: short duration vs. ultra-short duration: adjusted HR 1.68 (95% CI 1.62–1.75, p = 0.0001); long duration vs. ultra-short duration: adjusted HR 2.33 (95% CI 2.19–2.46, p = 0.0001); (ii) 70 days instead of 56 days: short duration vs. ultra-short duration: adjusted HR 1.53 (95% CI 1.47–1.59, p = 0.0001); long duration vs. ultra-short duration: adjusted HR 2.10 (95% CI 2.01–2.20, p = 0.0001).

Discussion

Main findings

A long duration of the index episode of antidepressant treatment was associated with an increased risk of reinitiation of antidepressant treatment, independently of the other characteristics. The association between duration of index episode and risk of reinitiation was found for all classes of antidepressants.

Methodological limitations

As no information on diagnosis was available in the database, indications for prescribing might be for psychiatric illnesses other than depression such as anxiety disorder, as well as for somatic illnesses. However, this limitation is shared by most observational studies on administrative databases since the reliability of diagnoses of depression is often questionable in such databases. For example, "feeling depressed" was included in the case definition of depression in the study by Gardarsdottir and colleagues [11]. Furthermore, the recommendation for duration of antidepressant treatment in depression applies to most other indications (particularly anxiety disorders), even if the prognostic impact of early discontinuation is less documented in the other indications.

Since patients were selected on the basis of a 6-month pre-treatment period without antidepressant dispensing, persons with pre-existing episodes of antidepressant prescribing were included. The duration of the pre-treatment period was similar to that used in all prior studies, except that by Gardarsdottir and colleagues who defined a 2-year antidepressant-free period [11,20]. This selection bias may have favoured the inclusion of persons at higher risk of relapse/recurrence. It might also have contributed to decreasing rather than increasing the differences

between the 3 groups, but it is unlikely to have changed the direction of the associations.

As no information on the actual duration of treatment was available in this administrative database, discontinuation of antidepressant treatment and occurrence of a new episode were estimated using information on dates of antidepressant dispensings. The gap length between prescriptions defined using this method is arbitrary and as a consequence highly variable from one study to another [21]. Methods using a short gap definition have a high sensitivity to identify relapse but little specificity, since an index episode with a short interruption may be misclassified as 2 distinct episodes. Conversely, methods using long gaps may misclassify true relapse as continuing index episode. We used a gap of intermediate duration (56 days without antidepressant prescribing) and used sensitivity analyses to confirm that the findings were not influenced by changing the gap definition.

Interpretation of findings

The paradoxical finding that early discontinuation of antidepressant treatment is associated with a decreased risk of reinitiation of antidepressant treatment is discrepant with results obtained by RCTs [4] and by most prior naturalistic studies [8–10]. However, this finding is in accordance with that recently reported by Gardarsdottir and colleagues [11]. These discrepancies are partly explained by methodological differences particularly in the definition of the period at risk of relapse [19]. This definition widely influences the findings in naturalistic studies exploring the impact of early discontinuation of antidepressant treatment. Studies showing a protective effect of long duration of treatment on the risk of recurrence have explored the risk of relapse/recurrence after a fixed period of 6 months starting at the onset of index episode [8–10]. The actual duration of the index episode was not taken into account, reducing the at-risk period for persons with longer duration (immortal time) and increasing it for persons with shorter duration (neglected time) [19]. These biases were better controlled by the method based upon the actual duration of the index episode used in the study by Gardarsdottir and colleagues [11] as well as in the present study.

We found that female gender, older age and low income were independently associated with an early risk of treatment reinitiation. Prior studies have reported that low socio-economic status and older age were associated with poorer outcome in persons with depression, but controversial findings have been found regarding the impact of gender [9, 22, 23]. The clinical characteristics independently associated with early risk of reinitiation of antidepressant treatment can be considered as markers of illness severity ("serious chronic illness" status, prescription by a private psychiatrist or a hospital practitioner, co-prescription of other psychotropic drugs). A noteworthy finding was that the association between duration of index episode and outcome was independent from these markers of illness severity. However, these characteristics were only indirect proxies of the clinical state of the patient. Different findings may have been obtained by exploring the impact of other clinical characteristics such as diagnosis, symptom severity and prior psychiatric history, which were not available in the present study.

If the association observed in naturalistic conditions between short duration of index antidepressant treatment and decreased likelihood of reinitiation of antidepressant treatment is not a spurious one, what are the most likely explanations? In real-life conditions, a large proportion of antidepressant users do not present with any identified psychiatric disorder [24]. As recently shown by a meta-analysis, false-positive clinical diagnoses of depression are more frequent in primary care than missed diagnoses [25]. Although we have no information on indications for prescribing in the present study, we speculate that early discontinued antidepressant treatments might have been frequently prescribed in persons with no clinical indication for these treatments, such as persons presenting with adaptation disorders or with sub-threshold anxiety or mood symptoms [25]. These persons may have rapidly stopped the treatment when their symptoms (spontaneously) disappeared, or for treatments shorter than one month may have never consumed the drug. Hence, the lack of prognostic impact of early discontinuation might be explained by the lack of clinical indication of antidepressant drugs in a significant proportion of index prescriptions. Another hypothesis might that early discontinuation is more likely to occur in persons with depressive episodes of mild/moderate intensity since the duration of such episodes is shorter than those of severe intensity [26]. In such a case, the association between duration of treatment and outcome may be linked to the severity of the index episode rather than to the lack of indication of index antidepressant treatment.

One could abruptly conclude that it may be a reasonable decision to interrupt a treatment that is not or no longer needed. However, the fact that early discontinuation of antidepressant treatment has apparently less dramatic outcome consequences in naturalistic conditions than in RCTs cannot be considered as reassuring from a public health point of view. If this finding is explained by a high frequency of prescriptions out of the range of the clinical indications for antidepressant drugs, this clearly implies that health resources are wasted [27]. Furthermore, reinitiation of antidepressant treatment was the only outcome explored, so we cannot exclude that persons using antidepressant drugs for a short period may have presented with other types of adverse outcome. For example, persons using antidepressants for less than one month are exposed to a peak of suicidal risk [28] without any benefit. Strategies aimed at optimizing the prescription of antidepressant drugs in real-life conditions should be developed further.

Acknowledgements

We acknowledge the members of the Department of Studies on Pathologies and Patients of the Social Security Insurance (*Département des Etudes sur les Pathologies et les Patients de la CNAMTS*), particularly Philippe Ricordeau who played a key role in conducting this study as well as Sophie Pépin, Odile Kusnik-Joinville and Anne Cuerq. The authors also thank Ray Cooke for supervising the English of this manuscript.

References

1 *Bauer M*, *Bschor T*, *Pfennig A et al*. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care. World J Biol Psychiatry 2007; 8: 67–104
2 *Anderson IM*, *Ferrier IN*, *Baldwin RC et al*. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. J Psychopharmacol 2008; 22: 343–396
3 *National Institute for Health and Clinical Excellence*. Depression: the treatment and management of depression in adults (update) (Clinical guideline 90) http://guidance.nice.org.uk/CG90 2009

4 *Geddes JR*, *Carney SM*, *Davies C et al*. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003; 361: 653–661
5 *Reid S*, *Barbui C*. Long term treatment of depression with selective serotonin reuptake inhibitors and newer antidepressants. BMJ 2010; 340: 752–756
6 *Tournier M*, *Cougnard A*, *Boutouaba-Combe S et al*. Duration of antidepressant drug treatment and its determinants in France [in French]. Encephale 2010, In press
7 *Olfson M*, *Marcus SC*, *Tedeschi M et al*. Continuity of antidepressant treatment for adults with depression in the United States. Am J Psychiatry 2006; 163: 101–108
8 *Melfi CA*, *Chawla AJ*, *Croghan TW et al*. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. Arch Gen Psychiatry 1998; 55: 1128–1132
9 *Sood N*, *Treglia M*, *Obenchain RL et al*. Determinants of antidepressant treatment outcome. Am J Managed Care 2000; 6: 1327–1336
10 *Claxton AJ*, *Li Z*, *McKendrick J*. Selective serotonin reuptake inhibitor treatment in the UK: risk of relapse or recurrence of depression. Brit J Psychiatry 2000; 177: 163–168
11 *Gardarsdottir H*, *van Geffen EC*, *Stolker JJ et al*. Does the length of the first antidepressant treatment episode influence risk and time to a second episode? J Clin Psychopharmacol 2009; 29: 69–72
12 *Kirsch I*, *Deacon BJ*, *Huedo-Medina TB et al*. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med 2008; 5: e45
13 *Fournier JC*, *DeRubeis RJ*, *Hollon SD et al*. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA 2010; 303: 47–53
14 *Martin-Latry K*, *Begaud B*. Pharmacoepidemiological research using French reimbursement databases: yes we can!. Pharmacoepidemiol Drug Saf 2010; 19: 256–265
15 *De Roquefeuil L*, *Studer A*, *Neumann A et al*. L'Echantillon généraliste de bénéficiaires: représentativité, portée et limites. [in French]. Pratiques et Organisations de Soins 2009; 40: 213–223
16 *WHO Collaborating Centre for Drug Statistics Methodology*. About the ATC/DDD system. Oslo, Norway, Norwegian Institute of Public Health; 2007
17 *StataCorp*. Stata Statistical Software: Release 9.0. College Station, Texas, Stata Corporation; 2005
18 *Hertz-Picciotto I*, *Rockhill B*. Validity and efficiency of approximation methods for tied survival times in Cox regression. Biometrics 1997; 53: 1151–1156
19 *Gardarsdottir H*, *Egberts TC*, *Stolker JJ et al*. Duration of antidepressant drug treatment and its influence on risk of relapse/recurrence: immortal and neglected time bias. Am J Epidemiol 2009; 170: 280–285
20 *Gardarsdottir H*, *Egberts AC*, *Heerdink ER*. Transitions from general practitioner to psychiatrist care (or vice versa) during a first antidepressant treatment episode. Pharmacopsychiatry 2010; 43: 179–183
21 *Gardarsdottir H*, *Souverein PC*, *Egberts TC et al*. Construction of drug treatment episodes from drug-dispensing histories is influenced by the gap length. J Clin Epidemiol 2010; 63: 422–427
22 *Burcusa SL*, *Iacono WG*. Risk for recurrence in depression. Clin Psychol Rev 2007; 27: 959–985
23 *Moller HJ*, *Schnitker J*, *Flurenbrock W*. Factors associated with response in depressed elderly outpatients treated with escitalopram in a naturalistic setting in Germany. Pharmacopsychiatry 2010; 43: 210–215
24 *Grolleau A*, *Cougnard A*, *Begaud B et al*. Congruence between diagnosis of recurrent major depressive disorder and psychotropic treatment in the general population. Acta Psychiatr Scand 2008; 117: 20–27
25 *Mitchell AJ*, *Vaze A*, *Rao S*. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet 2009; 374: 609–619
26 *Kessler RC*, *Berglund P*, *Demler O et al*. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). JAMA 2003; 289: 3095–3105
27 *Druss BG*, *Wang PS*, *Sampson NA et al*. Understanding mental health treatment in persons without mental diagnoses: results from the National Comorbidity Survey Replication. Arch Gen Psychiatry 2007; 64: 1196–1203
28 *Jick H*, *Kaye JA*, *Jick SS*. Antidepressants and the risk of suicidal behaviors. JAMA 2004; 292: 338–343