# Clinical research

# Pharmacological approaches to the treatment of complicated grief: rationale and a brief review of the literature

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## Introduction

Complicated grief (CG) is a debilitating condition that is estimated to affect 6% to 25% of individuals who experience the loss of a loved one.[1-3] Recent research indicates that CG-specific psychological interventions are effective in reducing symptoms of CG.[4] However, data is still scarce on the potential efficacy of medication strategies in the management of CG symptoms. Given that many of those suffering from CG do

Complicated grief (CG) is a common and often under-acknowledged cause of profound impairment experienced after the loss of a loved one. Although both clinical and basic research suggests that pharmacological agents might be of use in the treatment of CG, research on pharmacological approaches to this condition is still scarce. Three open-label trials and one randomized trial on bereavement-related depression suggest that tricyclic antidepressants may be effective, although they may be more efficacious for depressive symptoms than for grief-specific symptoms. Four open-label trials (total number of participants, 50) of selective serotonin reuptake inhibitors (SSRIs) have yielded results, providing very preliminary support that they might be effective in the treatment of CG, both as a stand-alone treatment and in conjunction with psychotherapeutic interventions. These more recent studies have shown an effect on both depression and grief-specific scales. Furthermore, therapeutic interventions for CG may be more effective in conjunction with SSRI administration. Given the small number of pharmacological studies to date, there is a need for randomized trials to test the potential efficacy of pharmacological agents in the treatment of CG.

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not access mental health services[5] and are thus more likely to only be seen by primary care physicians, there is a need to better understand which pharmacological interventions are most likely to be efficacious, and for research to provide an evidence base of randomized controlled trials examining the efficacy of these agents. In this brief review, the rationale for a pharmacological approach to treating CG and current available data will be highlighted. Finally, further avenues for research will also be explored.

## Rationale for a pharmacological approach to the treatment of complicated grief

### Clinical rationale

CG is currently being considered for inclusion as a formal disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5)*.[6-8] However, some authors have highlighted that CG shares common features with two other *DSM-IV* disorders, namely major depressive disorder (MDD) and post-traumatic stress disorder (PTSD).[6] Although most studies report that only a subset of individuals with CG meet criteria for MDD,[9-11] both CG and depression include symptoms such as crying, sadness (though not necessarily generalized), sleep disturbances, and suicidal ideation. Although the nature of the stressor is different in CG (losing a loved one as opposed to confrontation with a life-threatening situation in PTSD), individuals with CG have similarly experienced a major life stressor. Furthermore, both of these conditions share some symptoms in common such as intrusive memories, sleep disturbances, avoidance, and feeling estranged from others. PTSD and CG nonetheless have many differences as well; for example, while PTSD has been conceptualized as a fear-based disorder in response to traumatic experiences, CG has been conceptualized as resulting from a major attachment loss with associated difficulties processing the loss and adjusting to life without the deceased.[6] Over the past decade, antidepressants, and especially selective serotonin reuptake inhibitors (SSRIs), have been widely demonstrated to be effective in reducing both MDD symptoms[12] and PTSD symptoms,[13] including, sadness, suicidal ideation, and intrusive thoughts. In a meta-analysis examining the efficacy of pharmacotherapy in PTSD, Stein et al reported that SSRIs were more effective than placebo in reducing PTSD symptom

severity (weighted mean difference on the clinician-administered PTSD scale = -5.95, 95% confidence interval = -8.9 to -3.0, pooled n =1907), and in inducing treatment response (relative risk = 1.59, 95% confidence interval =1.39 to 1.82, pooled n =999).[13] Given the clinical overlap between CG and both MDD and PTSD, as well as the demonstrated broad efficacy of SSRIs across mood and anxiety disorders, it is hypothesized that SSRIs might also be effective for CG, a debilitating condition that shares symptoms with both MDD and PTSD and may be conceptualized as a stressor-induced affective syndrome.

### Neurobiological rationale

In an animal study, Fontenot et al reported that macaques exposed to a chronic social stress reminiscent of bereavement (ie, deprivation of social group members) exhibited significantly lower serotonin and serotonin metabolite levels in the prefrontal cortex compared with their counterparts who were not stressed by a similar deprivation.[14] These findings suggest that social stress following separation may result in a long-term reduction of serotoninergic activity in the brain. Thus, the loss of a close group member has been demonstrated to result in neurotransmitter changes in a brain region critical for executive and psychological functioning. Given the genetic and neurobiological similarities between macaques and humans, this might be considered as an animal model of CG.[15] In terms of neurobiological mechanisms, it thus appears that both depression and grief may share lower levels of serotonergic brain activity. In addition, it has been demonstrated in humans that subjects suffering from complicated grief (as opposed to simple uncomplicated grief) show differences in diurnal cortisol profiles,[16] also suggesting that complicated grief pathophysiology may involve some of the same molecular pathways as have been characterized for MDD.

In addition to the molecular changes described above, patients with complicated grief may have a pre-existing genetic vulnerability to suffering a more debilitating illness than those who experience uncomplicated grief. By playing a major role in the degradation of amines, the enzymatic activity of monoamine oxidase A (MAO-A) affects serotonergic neurotransmission. Recent research examining a genetic variation in the MAO-A gene also suggests that in the context of major depression, a cer-

tain variant of the MAO-A gene might be associated with the occurrence of complicated grief in women.[15] Taken together, these neurobiological and genetic findings provide early support that CG may be associated with certain alterations in the serotonergic neurotransmission systems, and that the pharmacological manipulation of these systems might provide a potential avenue for treating CG.

## Early research: bereavement-related depression

While research on the pharmacological treatment of CG has only recently emerged paralleling the progress in defining this condition, earlier work investigating the efficacy of antidepressants on bereavement-related depressive symptoms has yielded interesting results.

The first open-label antidepressant trial was conducted by Jacobs et al in a sample of 10 widows and widowers.[17] The authors reported that after 4 weeks of treatment with desipramine (75 mg to 150 mg/day), 4 of the participants were rated as "very much improved" and 3 as "much improved" on the Clinical Global Impression – Improvement (CGI-I) scale, while only one participant dropped out of the study due to side effects. Although this study also yielded significant reductions in depressive symptoms as measured by the Hamilton Depression Rating Scale (HDRS[18]) in these seven participants, only a subset of these responders (three out of seven) also experienced a significant improvement in grief intensity.[17]

A second open-label trial was also conducted in a sample of bereaved spouses. Pasternak et al investigated the potential efficacy of another tricyclic antidepressant, nortriptyline, on bereavement-related depressive symptoms, sleep and grief intensity.[19] The authors reported that, among the 13 participants, depressive symptoms measured by the HDRS and the Beck Depression Inventory (BDI[20]) and sleep quality assessed by the Pittsburgh Sleep Quality Index were significantly reduced after a median treatment period of 6.4 weeks. Similarly to Jacobs et al's study, results indicated some improvement in grief intensity as measured by the Texas Revised Inventory of Grief (TRIG[21]), although the clinical significance of this improvement was marginal (overall improvement rate of 9.3%).

Zisook et al reported results of another open-label trial of bereavement-related depression.[22] In this study, the authors did not investigate a tricyclic, but a newer-generation antidepressant. Within 8 weeks of losing their spouses,[22] participants were treated with 150 mg to 300 mg/day of buproprion SR. Fourteen of the subjects completed the 8-week trial (dropout rate =36%). Although no formal psychotherapy was provided, time was allocated during the sessions for listening to patients' concerns. Both study completers and the intention-to-treat sample showed statistically significant improvements in depressive symptoms as measured by the HDRS and the Clinical Global Impression-Severity (CGI-S). Regarding measures of grief intensity, both the completers and the intention-to-treat samples also showed statistically significant improvements on the Inventory of Complicated Grief (ICG[23]). While improvement on the TRIG was also significant in the intention-to-treat sample, there was only a trend towards significance in the completers sample. Again, improvement in grief intensity, although statistically significant in this study, seems to be quite modest relative to the improvement noted in depressive symptoms. In the intention-to-treat sample, after 8 weeks of treatment, CG symptoms decreased by 5% on the TRIG and 18% on the ICG, while depressive symptoms decreased by 54% on the HDRS.

Currently, results from only one randomized controlled trial of the pharmacological treatment of bereavement depression have been published.[24] Reynolds et al randomized 80 older adults to 16 weeks of either nortriptyline plus interpersonal therapy (n=16), placebo plus interpersonal therapy (IPT, n=17), nortriptyline alone (n=25), or placebo alone (n=22).[24] Participants were required to meet criteria for MDD plus a certain level of grief intensity as defined by a score on the TRIG of at least 45. Sixty-nine percent of the participants in the nortriptyline plus IPT achieved remission, defined by a score of 7 or below for 3 consecutive weeks on the 17-item HDRS, while 29%, 56%, and 45% achieved remission in the placebo plus IPT, nortriptyline alone and placebo alone groups, respectively. Controlling for age as a covariate, the authors found a significant effect of the nortriptyline, but no significant effect of IPT nor any additive effect for nortriptyline combined with IPT. However, the authors failed to demonstrate any differential effect of any of these treatments on improvement rates of grief intensity as measured by both the TRIG and the ICG. The main results from these studies are reported in *Table I*.

In summary, some evidence suggests that antidepressants, in particular tricyclics, may be effective for reduc-

ing depressive symptoms in bereavement-related depression, even if their effect might not be as dramatic or specific for grief intensity. Although these findings provide valuable information about the treatment of grief symptoms in the context of bereavement-related depression, it has been consistently shown that compli-cated grief is a clinical entity distinct from depression.[1] It is thus complicated to isolate the efficacy of pharma-cological treatments for grief symptoms in the context of co-occurring depression. As individuals with CG often present without meeting full criteria for depression, additional studies are needed to elucidate the efficacy of

| Authors (year) | Design | Population | Duration | Time since loss | Drug | Results |
|---|---|---|---|---|---|---|
| Bereavement-related depression | | | | | | |
| Jacobs et al (1987)[17] | Open-label (ITT) | n=10, age range=26-65, 80% women | 4 weeks | | Desipramine, 75-150 mg/day | Depressive symptoms: 70% responders Grief symptoms: 37.5% responders |
| Pasternak et al (1991)[19] | Open-label (SC) | n=13 CG patients, 61.5% women, mean age=71.1 | median= 6.4 weeks | mean= 11.9 months | Nortriptyline mean dose= 49.2 mg/day | Depressive symptoms improvement rate: 68% Grief symptoms improvement rate: 9% |
| Zisook et al (2001)[22] | Open-label (ITT) | n=22 for ITT sample, 77.3% women, mean(SD) age=63.5 (11.0) | 8 weeks | 4-6 weeks | Bupropion, flexible 150-200 mg/day | ITT: Depressive symptoms improvement rate: 54% ITT: Grief symptoms improvement rate: ICG= 18%, TRIG= 5% |
| | Open-label (SC) | n=14 for SC sample | 8 weeks | 4-6 weeks | Bupropion, flexible 150-200 mg/day | SC: Depressive symptoms improvement rate: 73% SC: Grief symptoms improvement rate: ICG=22%, TRIG-9% |
| Reynolds et al (1999)[24] | RCT | n=25 nortriptyline vs n=22 placebo (vs n=17 IPT vs n=16 nortriptyline+IPT), Major Depressive Disorder, TRIG≥45, 72.5% women, mean age=66.1 | 16 weeks | mean=8.1 months | Nortriptyline, mean dose= 66 mg/day | Depressive symptoms: nortriptyline group=56% remission placebo group=45% remission vs nortriptyline+IPT group=69% remission Grief symptoms: no differential effect of treatments |
| Complicated grief | | | | | | |
| Zygmont et al (1998)[25] | Open-label (SC) | n=15 mean age=57, icg≥20, 73.3% women | 16-week | median =17 months | Paroxetine, flexible 20-50 mg/day | Depressive symptoms improvement rate: 51% Grief symptoms improvement rate: ICG=48% |
| Shear et al (2006)[28] | Open-label (modified ITT) | n=17, ICG≥30 | 16 weeks | mean=3.9 years | Escitalopram, flexible 10-20 mg/day | ITT: Grief symptoms improvement rate: ICG=24% |
| | Open-label (SC) | n=7, ICG≥30 | | | | SC: Grief symptoms improvement rate: ICG=35% |
| Simon et al (2007)[26] | Case series | n=4, ICG≥25, 100% women, mean (SD) age=41.75 (14.4) | 10 weeks | > 6 months | Escitalopram, flexible 10-20 mg/day | Complicated grief: 100% responders Grief symptoms improvement rate: ICG=76% |
| Hensley et al (2009)[27] | Open-label (SC) | n=14 with Major Depressive Disorder and CG | 12 weeks | > 6 months | Escitalopram, flexible 10-20 mg/day | Grief symptoms improvement rate: ICG=21% |

**Table I.** Summary of results of medication trials in bereavement-related depression and complicated grief. CG, complicated grief RCT, randomized controlled trial; SC, study completers; ITT, intention to treat; TRIG, Texas revised inventory of grief; ICG, inventory of complicated grief

pharmacological treatments for CG, both with and without MDD comorbidity to better characterize the effects on grief specific symptoms.

## Pharmacological approach to the treatment of complicated grief

Pharmacological trials of complicated grief (also formerly known as "prolonged grief disorder" or "traumatic grief") are scarce, likely in part because attention to this condition as a potential formal diagnostic entity has only recently occurred, with different criteria sets proposed that are still the focus of ongoing debate.[6] Further, the lack of inclusion of CG in the *DSM* as a formalized diagnosis to date has implications for FDA trials and limits pharmaceutical development targeting CG. Also, without a formalized diagnosis, few patients are assessed for CG, and clinicians do not have CG-specific billing codes, together limiting targeted treatment and naturalistic study of pharmacotherapy already administered to help seeking patients in practice settings. This issue is of critical importance to debates about whether CG should be included in *DSM-5*.

### Selective serotonin reuptake inhibitors

One publication has reported a post-hoc comparison of paroxetine and nortriptyline for the treatment of traumatic grief (an earlier term in the literature for CG). Zygmont et al examined open paroxetine (flexible dosing, 10 mg to 50 mg/day) administered for 16 weeks to 21 individuals with traumatic grief simultaneously participating in a psychotherapy treatment development study.[25] Fifteen participants completed at least 6 weeks of medication, and 13 the full course of the trial (16 weeks). In this study, measures of grief intensity (using the ICG) and measures of depression (using the HDRS rating scale) both declined by 48% and 51% respectively in the paroxetine-treated groups. This study also compared these results with an ongoing study of bereavement related depression in which patients were treated with nortriptyline (with and without psychotherapy; n=22 for at least 6 weeks, n=18 for 16 weeks). Again, both of the antidepressant-treated groups showed significant reductions in both grief and depressive symptoms (using the ICG and HDRS rating scales), even though depressive symptoms responded earlier in the treatment course than the improvement in grief symptoms.

In another uncontrolled study, Simon et al treated and prospectively assessed four women with a primary diagnosis of CG (defined as a score of 25 or above on the ICG, at least 6 months after the death of a loved one), treated with escitalopram.[26] At the end of the 10-week trial, all participants were rated as "very much improved" on the CGI-I. Both complicated grief symptoms assessed by the ICG and depressive symptoms as assessed by the HDRS were significantly decreased.

A more recent open-label study investigating the potential efficacy of escitalopram was conducted in 30 individuals with bereavement-related depression.[27] In this trial, participants meeting criteria for MDD after the loss of a loved one were treated for 12 weeks with a mean final dose of 13.1 mg/day of escitalopram. Of the 29 individuals studied, 14 were diagnosed with complicated grief in addition to MDD, whereas 15 of the subjects met criteria for MDD but not for CG. When the results of treatment were analyzed by CG diagnosis, mean ICG scores improved by 21% in the CG group, and by 39% in the uncomplicated grief group. Given the small sample size, however, this difference was not statistically significant. Defining treatment response as "very much improved" and or "much improved" on the CGI-I scale, 45% of the whole sample were responders in terms of grief symptoms, and 83% in terms of depressive symptoms.

Another open-label trial[28] was conducted in 17 participants with CG (scoring ≥30 on the ICG, more than 6 months after a loss) as a primary disorder. Participants received escitalopram 10 mg/day, with an option to increase the dose to 20 mg/day, at week 4. At 16 weeks, the response rate was of 38% with a decrease in mean ICG score of only 24% in the intention-to-treat sample (those who attended at least one session). The main results from these studies are reported in *Table I*.

### Other medications

To the best of our knowledge, there is no report on the primary efficacy of benzodiazepines for the treatment of CG. However, an earlier randomized controlled trial has investigated the use of diazepam vs placebo in the medical management of recent grief.[29] In this study,[30] recently bereaved individuals were randomized to receive a bottle containing 20 tablets of either diazepam (2 mg) or placebo for PRN use during the following 6 weeks. At the 7-month follow-up, analyses failed to show any significant

differences between the two groups in terms of grief symptom severity as measured by the Bereavement Phenomenology Questionnaire (BPQ[30]). Interestingly, those receiving diazepam had more sleep problems than those assigned to placebo. This is consistent with research on PTSD suggesting that benzodiazepines might actually increase the severity of PTSD.[31-33] Furthermore, recent data suggests that the use of benzodiazepines in the aftermath of a loss might also lead to long-term prescription dependence in elderly individuals.[34]

## Combining pharmacological and psychological interventions

In their 2001 publication, Zisook et al reported that during their trial, several patients specifically stated that the treatment of depressive symptoms allowed them "to grieve more intensely" and "confront situations that they had been avoiding when more depressed." [22] This suggests that a concurrently prescribed antidepressant might improve outcomes with psychological grief specific interventions based on behavioral techniques. As summarized above, an earlier study by Reynolds et al[24] failed to show a significant interaction effect of nortriptyline and interpersonal therapy for the treatment of bereavement-related depression. However, in Shear et al's randomized controlled trial of complicated grief therapy (CGT) vs interpersonal therapy for loss (IPT) in complicated grief[35] in which stable medication was allowed during the course of the study, concomitant antidepressant use was marginally associated with a better outcome in each arm (for both CGT and IPT). In follow-up analysis, Simon et al more closely examined medication effects based on data obtained from the same sample.[36] Although results for each group were only marginally significant, they reported that in the full sample (n=95), even after controlling for covariates (age, gender, race, and psychiatric comorbidity), participants who were prescribed a stable dose of antidepressant during the trial were more than two times more likely to be treatment responders ("very much improved" and or "much improved" on the CGI-I scale) than those who were not (adjusted odds ratio=2.7, 95% confidence interval (CI)=1.1 – 6.8). Furthermore, examination of dropout rates revealed that use of antidepressants was associated with a sixfold increased rate of study completion in the CGT arm (adjusted for psychiatric comorbidity odds ratio=6.3, 95%CI=1.2 – 34.2). However, antidepressant use was not associated with such an increase in study completion rate in the group allocated to IPT. Thus it appears that antidepressant treatment may allow participants to engage more fully or complete participation in CG specific psychotherapy interventions as compared with those treated with therapy alone, although conclusions are limited by the naturalistic, open nature of medication prescribing in this sample. The authors also examined the effect of naturalistic prescription of stable doses of benzodiazepines. Benzodiazepine use was significantly associated with an increase in treatment response rate in the IPT group, but not in the CGT group, nor in the whole sample. The use of benzodiazepines was not significantly associated with dropout rates in either group.

## Summary and future directions

Although similar overlapping entities such as pathological grief have long been described in the psychological and psychiatric literature, formalized diagnostic criteria for CG have only been recently proposed and are not yet part of the formal diagnostic nomenclature, limiting the development of an evidence base for targeted pharmacotherapy interventions. To date, randomized controlled research is only available for the efficacy of specific psychological interventions to treat this condition.[35] Though there have been some open-label and small studies on pharmacological interventions, well-designed and powered efficacy studies on the pharmacological treatment of this condition are still lacking. Results from several open-label studies suggest that while tricyclic antidepressants might not be specifically efficacious for grief symptoms, SSRIs might be of potential use in the management of this debilitating condition, both as standalone treatments or in conjunction with specific psychotherapies. A large multisite randomized controlled trial is currently underway testing the differential efficacy of citalopram, citalopram plus CGT, and CGT plus pill placebo versus pill placebo.[37]

Recent advances in our understanding of the neurobiology of CG may also help develop innovative treatment strategies. Complicated grief has been hypothesized to involve reward-related brain systems that have been suggested to be related to attachment behavior.[38] A recent neuroimaging study found that, while both individuals with noncomplicated grief and those with CG display activity in pain-related neural networks in response to

reminders of the deceased, reward-related activity in the nucleus accumbens was only found in those with CG.[39] This result is similar to that reported in studies on addiction and indicates that the absence of successful adaptation after a loss may involve persistent "craving" mechanisms. Activity in the nucleus accumbens, which plays a central role in the reward system, has been shown to be intimately linked to increased dopaminergic activity.[40] Attempts to pharmacologically treat addiction with dopaminergic agents have previously been tried. To date, however, trials of dopaminergic antagonists (ie, antipsychotic agents) in the treatment of substance-related disorders have yielded mixed results with, for example, positive results of quetiapine on craving in alcohol dependence[41,42] contrasting with negative results of olanzapine and risperidone in cocaine dependence.[43,44] Nonetheless, these preliminary data suggest that pharmacological manipulation of craving might be possible and that agents targeting dopaminergic transmission theoretically might be of potential use in the treatment of complicated grief when craving and longing are the core symptoms. However, to date, there is clearly no current indication for the use of antipsychotics as a primary treatment for CG, and given their safety profiles they are unlikely to be a first-line approach in the future.

Finally, recent research also suggests that CG symptoms may be associated with specific physiological[45] and biological features[16] that might provide insight into novel treatment approaches. In particular, Bonanno et al[45] reported that CG symptoms were associated with decreased heart rate reactivity when talking about the deceased one, suggested that sympathetic or parasympathetic activity might be involved in the pathophysiology of CG and that pharmacological manipulation of these systems might also be a potentially interesting treatment approach.

## Conclusions

There is some tantalizing early data suggesting that treatment with an SSRI may improve both the depressive and grief-specific symptoms experienced in complicated grief. Furthermore, antidepressant administration may make therapeutic interventions more effective. Further studies on the role of antidepressants are indicated before definitive conclusions may be drawn, as well as research examining the role of other neurotransmitter systems and stress pathways to better elucidate the biology and pharmacotherapy of complicated grief. ❏

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# Clinical research

## Propuestas farmacológicas para el tratamiento del duelo complicado: razones principales y una breve revisión de la literatura

*El duelo complicado (DC) es una causa común y a menudo subestimada de deterioro profundo que se experimenta después de la muerte de un ser querido. Aunque la investigación clínica y básica sugiere que los fármacos pueden ser útiles en el tratamiento del DC, todavía es escasa la investigación sobre los aspectos farmacológicos de este cuadro. Tres estudios de diseño abierto y uno randomizado sobre la depresión asociada con el duelo sugieren que los antidepresivos tricíclicos pueden ser efectivos, aunque ellos pueden resultar más eficaces para los síntomas depresivos que para los síntomas específicos del duelo. Cuatro estudios de diseño abierto (con un total de 50 participantes) de inhibidores selectivos de la recaptura de serotonina (ISRS) han obtenido resultados, proporcionando una base muy preliminar sobre la eficacia en el tratamiento del DC, ya sea empleados en forma exclusiva o en combinación con intervenciones psicoterapéuticas. Estos estudios más recientes han mostrado un efecto en las escalas de depresión y aquéllas específicas para duelo. Además las intervenciones terapéuticas para el DC pueden ser más efectivas cuando se combinan con la administración de ISRS. Dado que a la fecha se dispone de pocos estudios farmacológicos, se requiere de estudios randomizados para evaluar la potencial eficacia de los fármacos en el tratamiento del DC.*

## Traitements pharmacologiquesdu deuil compliqué : argumentaire et brève revue de la littérature.

*Le deuil compliqué (DC) est une cause courante et souvent méconnue d'incapacité importante après la perte d'un être aimé. La recherche, qu'elle soit clinique ou fondamentale, suggère que des traitements pharmacologiques pourraient être utilisés dans ce contexte mais elle est encore pauvre sur ce sujet. D'après trois études en ouvert et une étude randomisée sur la dépression liée au deuil, les antidépresseurs tricycliques pourraient être efficaces bien qu'ils soient plus actifs sur les symptômes dépressifs que sur les symptômes spécifiques du DC. Les résultats très préliminaires de quatre études en ouvert (nombre total de participants, 50) sur les inhibiteurs sélectifs de la recapture de la sérotonine (ISRS) montrent qu'ils pourraient être efficaces dans le traitement du DC à la fois en traitement unique et en association à des actions psychothérapeutiques. Ces études plus récentes ont montré un effet sur les échelles à la fois de la dépression et celles spécifiques du DC. De plus, les approches thérapeutiques du DC peuvent voir leur action renforcée par l'administration simultanée d'ISRS. Compte tenu du faible nombre d'études pharmacologiques à ce jour, d'autres études randomisées sont nécessaires pour évaluer l'efficacité potentielle des agents pharmacologiques dans le traitement du DC.*

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