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CLINICAL REVIEW

Dreaming under antidepressants: A systematic review on evidence in depressive patients and healthy volunteers

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SUMMARY

Sleep related symptoms of depression include sleep fragmentation, early morning awakening, decreased rapid eye movement (REM) sleep latency, increased REM density, and more negative dream content. Most tricyclic antidepressants (ADs) increase total sleep time and decrease wake time after sleep onset, while many selective serotonin reuptake inhibitors (SSRIs) have an opposite effect. However, almost all ADs prolong REM sleep latency and reduce the amount of REM sleep. Case reports and research data indicate a strong effect of ADs on dream recall and dream content. We performed a systematic review (1950 to August 2010) about ADs impact on dreaming in depressive patients and healthy volunteers. Twenty-one clinical studies and 25 case reports were eligible for review and document a clear AD effect on dreaming. The major finding, both in depressed patients and in healthy volunteers, is a decrease of dream recall frequency (DRF) under ADs. This is a rather consistent effect in tricyclic ADs and phenelzine, less consistently documented also for SSRIs/serotonin norepinephrine reuptake inhibitors (SNRIs). Tricyclic ADs induce more positive dream emotions. Withdrawal from tricyclic ADs and from the monoamine oxidase inhibitors phenelzine and tranylcypromine may cause nightmares. Intake and even more withdrawal of SSRIs/SNRIs seem to intensify dreaming, which may be experienced in different ways; a potential to cause nightmares has to be taken into account. Though there are clear-cut pharmacological effects of ADs on DRF and dream content, publications have been surprisingly scarce during the past 60 years. There is evidence of a gap in neuropsychopharmacological research. AD effects on dreams should be recognized and may be used in treatment.

Introduction

Antidepressants (ADs), besides antihyperlipidemic agents and analgesics, are the most prescribed drugs in the U.S.[1] In 2006, the prevalence of a lifetime experience of a depressive disorder was 15.7% among U.S. residents aged 18 or older; a 35% increase is expected by 2050.[2] The estimated economic burden of depression in the U.S. rose from $77.4 billion in 1990 (inflation-adjusted dollars) to $83.1 billion in 2000.[3] Although ADs have a strong impact on sleep and also on dreaming,[4,5] the magnitude and characteristics of AD influence on dreaming have found little attention in efforts to map AD effects.

The importance of ADs is highlighted not only by their therapeutic use for depressive disorders but also by their use in a variety of diseases with impact on the mental state such as insomnia, anxiety disorder, post-traumatic stress disorder (PTSD), obsessive-compulsive disorder, and chronic pain.[6,7] Furthermore, there is an increasing field for cognitive enhancing and lifestyle use of ADs.[8]

One of the primary features of depression is disordered sleep. At the subjective level, depression is associated with insomnia,[9] difficulty in falling asleep, frequent nocturnal awakenings, non-restorative sleep, and early morning awakening. Reduction of rapid eye movement (REM) sleep latency is one of the most robust and specific features of sleep in depressed patients and considered a trait marker of depression.[10–12] Numerous other polysomnographic features of altered sleep in depression have been documented, such as increases in REM density, duration of first REM sleep period, time of REM sleep, sleep latency, as well as waking

Abbreviations: AD, antidepressant; DRF, dream recall frequency; ICSD-R, international classification of sleep disorders, revised; PTSD, post-traumatic stress disorder; RBD, REM sleep behavior disorder; REM, rapid eye movement; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor.

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time, and decreases in total sleep time, slow wave sleep, sleep continuity, and sleep efficiency.[4,9,13]

Successful improvement of depressive mood by treatment with ADs may be accompanied by different effects on sleep. Triciyclic ADs tend to improve sleep quality and total sleep time,[14] while most selective serotonin reuptake inhibitors (SSRIs) tend to cause insomnia and to reduce total sleep time.[15] The effects of most ADs on REM sleep are strong and relatively consistent: a prolongation of REM sleep latency and a reduction of REM sleep time.[4,16–19] In patients with depression and reduced REM latencies, amitryptiline induced REM sleep suppression during the first two treatment nights, correlated with good clinical response.[14,20] However, this finding was not consistently confirmed.[21] Monoamine oxidase inhibitors may virtually eliminate REM sleep,[19,22,23] a phenomenon that neither necessarily produces a positive clinical response in patients nor causes obvious harm.[19]

The following features have been described in dreams of depressive patients: reduced dream recall frequency (DRF),[24,25] reduced length of reports,[26,27] dream contents ranging from "mundane",[26,28] "trivial",[26] to increased "masochistic",[29–32] vivid, disturbing, and sometimes emerging as nightmares.[9] In psychotherapeutic settings, dream content correlated with therapy outcome. In depressed female divorcees, an increase in masochism across the night was a poor prognostic sign.[31] Depressed divorcees who incorporated the loss in their dreams and had stronger affects in dreams were finally better adjusted to their new life.[33] High masochism scores in dreams of depressed women were related to a decreased likelihood of clinical improvement.[32] Even after full clinical remission for at least six months and no chronic use of psychotropic drugs for at least two months, formerly depressive patients still showed significant negative features in REM dreams.[30] This included: increased masochism, increased hostility in the environment, more inanimate objects exerting physical effort, more dreaming of the past, and shorter narratives.[30]

Rationale

Negatively altered dreams are a concomitant phenomenon of depressive disorders. The study of dream in a disease context has a long tradition, primarily in psychoanalysis. After the discovery of REM sleep[34] with its undeniable link to dreams and after development of AD drugs, clear-cut data emerged that depression is accompanied by reduced REM sleep latency and increased REM sleep density[35] and that most ADs have a strong REM sleep reducing effect. REM sleep reduction by ADs may have a significant impact on dreaming; interestingly, the magnitude and characteristics of this phenomenon have hardly been determined until now.[36–39] Considering on the one hand the epidemiological importance of depression and long-term AD treatment, and on the other hand depression as a mental disorder with negatively toned thinking and dreaming, this systematic review was designed to document the state of evidence regarding impact of ADs on dreaming in depressed adults and in healthy volunteers.

Methods

A systematic review[40] was performed, screening the data sources Ovid MEDLINE, Cochrane Library, PsycNET/PsycINFO, Virtual Health Library, and clinical trial register websites (e.g., clinicaltrials.gov, apps.who.int/trialsearch) for articles in English, German, Spanish, Portuguese, French, and Italian. Used search terms were "dream*(-s, -ing)", "nightmare*(s)", and "antidepress*(-ant, -ants, -ive)", the observation period was 1950 to August 2010. To identify further studies, reference lists of articles and books were scanned.[41,42] Three inclusion criteria were used. I) Only clinical and case studies were included with adult depressive patients or mentally healthy volunteers older than 18 years. Minimum requirements were: II) two phases of a) off- and on-drug states with at least one AD or of b) comparison of at least two ADs; and III) structured reporting on dreaming under both treatment conditions. Studies on diseases other than depression were excluded. Eligibility assessment was performed by two independent, unblinded reviewers according to standardized protocol. Disagreements between reviewers were resolved by consensus.

Studies meeting inclusion and exclusion criteria after structured data extraction were evaluated in the following dimensions:

A) Characteristics of participants: number of patients and volunteers, gender, age.
B) Sources of dream reports: induced REM sleep awakenings, daily diary, full length reports, scores, structured questions, unstructured interviews.
C) Antidepressants: substances, dosages, phases of administration.
D) Quantitative results: DRF, word count, descriptive data.
E) Qualitative results: score results, descriptive data.
F) Possible links between: clinical improvement and change in dream characteristics.

The reviewed studies were grouped as follows:

A) studies using induced REM sleep awakening;
B) studies using a daily diary on dreaming;
C) and D) studies using neither induced REM sleep awakening nor a daily diary, but reporting on dream data as C) a major or D) an additional study outcome; and
E) case studies.

Results

Using the search terms "dream*(-s, -ing)", "nightmare*(s)", and "antidepress*(-ant, -ants, -ive)", Ovid MEDLINE retrieved 97 abstracts; three of them double citations, 10 reviews, and 35 not fulfilling abstract screening criteria (investigating PTSD 9, medications other than ADs 6, children 5, narcolepsy 4, Parkinson's disease 2, schizophrenia 2, other reasons 7). The remaining 49 papers were full-text screened and 28 full papers were considered suitable for structured data extraction according to protocol criteria. Further 32 papers which meet these criteria were found: four in other databases (two each in PsycNET and Virtual Health Library), two in congress volumes, and 26 papers via references of articles and books.

These 60 full papers were data extracted in a structured approach according to protocol. Three clinical studies did not fulfill the criteria for review due to mixed disease groups. The remaining 57 full papers were included in the review, consisting of 46 study main publications and 11 double or additional publications (nine clinical studies and two case studies). The 46 studies included in that review consist of: 21 clinical studies and 25 case studies.

The 21 clinical studies provide material for the review from:

A) Four studies based on induced REM sleep awakenings;
B) Eight studies using a daily diary with data on dreaming (also including one study from group A[43]);
C) Four studies reporting on dream data as a major study outcome (using at least two scales or two structured questions, but neither induced REM sleep awakening nor a daily diary);
D) Six studies reporting on dream data as an additional study outcome to other major study aims (using one scale or

structured question or an unstructured interview, but neither REM sleep awakening nor a daily diary).

The 25 case studies provide material for the review from:

E) Clinical interviews.

If not otherwise specified, changes are compared against a non-drug state (pre phase or withdrawal) and results from the clinical studies are only reported, if the level of statistical significance is $p<=0.05$.

Clinical findings

Four clinical studies based on induced REM sleep awakenings[43–46] (Table 1); additional publications[47–51]

Imipramine reduced DRF in healthy volunteers[44] but not in another study with depressive patients.[45] These two studies had seven content rating scales in common but found different results: imipramine increased hostility per word of dream report in healthy volunteers only,[44] while the same substance increased heterosexuality contents and reduced anxiety only in depressive patients.[45] Depressive patients taking different tricyclic ADs reported a reduction of unpleasant feelings as well as a reduction of family members as compared to friends and strangers.[46] The rest of the content scales used in these four studies showed no significant differences under the studied tricyclic ADs. This also includes the extensive, amitriptyline implementing study of Hartmann and Cravens,[43] which used various content rating scales, two nights with REM sleep awakenings, and a 60-day diary. However, it[43] could not document a single significant difference in any of these parameters measured.

Eight clinical studies using a daily diary with data on dreaming[19,43,52–57]; additional publications[47,48,58,59]

In a very comprehensive study by Pace-Schott et al.,[57] 14 healthy volunteers on either fluvoxamine or paroxetine reported: increases in visual vividness, emotional intensity, and meaningfulness; and during withdrawal from these two SSRIs: increases in memorability, visual vividness, and amount of sound. Withdrawal from fluvoxamine but not from paroxetine increased word count per dream and bizarreness.[57] DRF was decreased in this study administering either fluvoxamine or paroxetine[57] and in another study administering phenelzine (DRF 40.1% ± 13.7% before and 3.3% ± 3.3% on phenelzine treatment in six clinical responders out of 11 depressive patients).[19] Hartmann and Cravens[43] could not find any significant effect of amitriptyline on dreaming (details see group A). Only descriptive data (no level of significance reported) are reported from the other five studies of that diary using group.[52–56] A second study on phenelzine in depressive patients reported definitely no dream during intake of that substance, while these patients had "many dreams" during the pre-drug phase and "frequently reported dreams, many of which were frightening" during the withdrawal phase.[53] Taking imipramine, dream activity of healthy volunteers was summarized as: "diminution of dreaming when first on the drug, and an increase to a peak after the fourth withdrawal night".[52] Receiving bupropion, one participant out of eight healthy volunteers reported "vivid dreams".[56] Two tricyclic ADs using studies compared the impact of daily single bedtime dosages vs. daily multiple dosages,[54,55] measuring the percentage of nightmares in all reported dreams: under single bedtime dosages of tricyclics 78,6%[54] and 47%[55] of all dreams were nightmares, whereas under daily multiple dosages only 11,5%[54] and even 0%[55] were nightmares.

Four clinical studies reporting on dream data as a major study outcome (using at least two scales or two structured questions, but neither induced REM sleep awakening nor a daily diary)[24,39,60,61]; additional publications[26,62]

DRF was reduced in 1179 depressive patients on trimipramine[39] and in 21 patients on fluoxetine or nefazodone.[24] In 15 depressive patients presenting features suggestive of RBD (REM sleep behavior disorder) under treatment with SSRIs or SNRIs (serotonin norepinephrine reuptake inhibitors), change of treatment to no AD or to bupropion resulted in a lower frequency of nightmare recall and of dream enactment.[61] Dream emotions were more pleasant on trimipramine.[39] The study using fluoxetine or nefazodone concluded "dream content very similar to baseline"; but it also reported reduced results in five out of 18 implemented content scales, i.e., vividness, number of others, body presence, sexual content, and number of scenes.[24] A highly descriptive study on 52 depressive patients treated with different ADs found both frequency and activation of dreams unchanged.[60]

Six clinical studies reporting on dream data as an additional study outcome to other major study aims (using one scale or structured question or an unstructured interview, but neither REM sleep awakening nor a daily diary)[63–68]

Tianeptine as compared to amitriptyline intake resulted in an increase of "insomnia or nightmares".[66] Mianserine as compared to the pre-drug phase and to fluoxetine treatment reduced "dream activity".[67] 50% of patients on bupropion reported "vivid imagery and dreams" vs. only 8% of patients treated with different tricyclic or tetracyclic ADs (no level of significance reported).[63] Further three studies reported descriptive results on dream quality (no levels of significance stated).[64,65,68] On trimipramine, "very lively, intense dreams" with an emotional content neutral to positive and themes from childhood were frequently reported.[65] Withdrawal from amitriptyline produced complaints of "dream disturbance" in eight of ten depressive patients during the first few weeks.[64] 2.6% of patients reported "abnormal dreams" during withdrawal from desvenlafaxine vs. only 0.5% of patients during withdrawal from placebo.[68]

Twenty-five case studies reporting dream data from patient interviews[69–93] (Table 2); additional publications[94,95]

Most case reports are about negative impact of AD therapy or withdrawal on dreaming. Clear nightmares, an intensification of dreaming in a negative way or both these phenomena are reported by 27 of a total of 35 case study participants.[69–72,74–79,81,82,84–92] These negative effects were caused in 13 participants by AD therapy[81,82,84–92] and in 14 participants by AD withdrawal.[69–72,74–79] Three participants reported a neither negatively nor positively (emotionally undetermined) experienced intensification of dreaming.[72,73,83] A positive intensification of dreaming was reported in one publication with four cases taking fluoxetine.[80] However, out of seven other cases on fluoxetine, six participants reported clear nightmares, an intensification of dreaming in a negative way or both phenomena,[81,82,84,91] and one participant reported an emotionally undetermined intensification of dreaming.[83] Withdrawal of phenelzine resulted in nightmares in five participants[72,76,77] and in another participant in an emotionally undetermined intensification of dreaming.[72] Four depressive patients developed or perhaps unmasked RBD or RBD-like symptoms (intense dreams, themes of fighting, dream enacting, REM sleep without atonia documented in three[86,89,91] patients) apparently as a consequence of a newly established AD therapy. The reported substances in these cases are the SSRIs fluoxetine[91] and paroxetine,[89] the SNRI venlafaxine,[86] and the tetracyclic mirtazapine.[92] In one depressive patient bereavement nightmares ceased under therapy with sertraline.[93]

Table 1
Twenty-one clinical studies reporting dream data under antidepressants in depressive patients and in healthy volunteers.

	Pat.	Healt.	Fem.	AD	Methods	Results
A. Four clinical studies based on induced REM sleep awakenings						
1961 Whitman et al.[44]	0	10	5	Imipramine	Sleep lab, 2 nights, induced awakening, full length dream reports, 7 content scales	ON: ↓DRF* ↑hostility per word*
1968 Kramer et al.[45]	10	0	5	Imipramine	Sleep lab, 5 nights, induced awakening, full length dream reports, 10 content scales	ON: ↑heterosexuality* ↓anxiety*
1974 Hartmann & Cravens[43]	0	10	0	Amitriptyline	Sleep lab, 2 nights, induced awakening, full length dream reports, many content scales, diary, 60 nights	ns
1978 Bollea et al.[46]	10	0	7	Amitriptyline, chlorimipramine, imipramine	Sleep lab, 4 nights, induced awakening, full length dream reports, 13 content scales, word count	ON: ↓unpleasant feelings* ↓family members vs. friends and strangers*
B. Eight clinical studies using a daily diary with data on dreaming						
1971 Oswald et al.[52]	0	6	0	Imipramine	Diary, 48 nights, 1 VAS ("absolutely dreamless" to "vivid dreaming all the time")	ON: diminution of dreaming WDRA: increase of dreaming with peak after fourth night
1971 Wyatt et al.[53]	6	0	5	Phenelzine	Diary, 57-101 nights, 1 question (presence or absence of dreaming)	PRE: "many dreams" ON: no dream reports WDRA: "frequently reported dreams, many of which were frightening"
1974 Hartmann & Cravens[43]	0	10	0	Amitriptyline	Diary, 60 nights, further details see group A	ns
1976 Flemenbaum[54]	76	0	nd	Tricyclic ADs	Diary, >= 6 nights, 2 questions (frequency of dreaming and of nightmares)	Higher percentage of nightmares under single bedtime AD dosage vs. multiple daily AD dosages (78.6% vs. 11.5%)
1978 Strayhorn & Nash[55]	48	0	nd	Tricyclic ADs	Diary, 7 nights, 2 questions (frequency of dreaming and of nightmares)	Higher percentage of nightmares under single bedtime AD dosage vs. multiple daily AD dosages (47% vs. 0%)
1985 Posner et al.[56]	0	8	0	Bupropion	Diary, 14 nights, side-effect check list	ON: vivid dreams in one subject
2001 Landolt et al.[19]	11	0	5	Phenelzine	diary, 35 nights, DRF	ON: DRF↓ in clinical responders*, ns in non responders
2001 Pace-Schott et al.[57]	0	14	10	Fluvoxamine, paroxetine	Diary, 31 nights, full length dream reports, DRF, 11 content scales, word count	ON: ↓DRF* ↑visual vividness* ↑emotional intensity* ↑meaningfulness* WDRA: ↑word count (result of fluvoxamine WDRA)* ↑memorability* ↑visual vividness* ↑amount of sound* ↑bizarreness (result of fluvoxamine WDRA)*
C. Four clinical studies reporting on dream data as a major study outcome (using at least two scales or two structured questions, but neither induced REM sleep awakening nor a daily diary)						
1970 Tölle & Crome[60]	52	0	36	Amitriptyline, protriptyline, imipramine, clomipramine, trimeprimine	Interview, 2 questions (frequency of dreams, activation of dreams)	ON: "unchanged"
1995 Armitage et al.[24]	21	0	12	Nefazodone, fluoxetine	Full length dream reports on non-consecutive mornings, DRF, 18 content scales, word count	ON: ↓DRF* ↓vividness* ↓number of others* ↓body presence* ↓sexual content* ↓number of scenes*
2009 Schredl et al.[39]	1179	0	732	Trimipramine	Interview, 2 questions (DRF over the last week by a four-point scale and general emotional tone of dreams by a VAS)	ON: ↓DRF* ↑pleasantness*
2010 Lam et al.[61]	15	0	10	SSRI / SNRI vs. bupropion / no AD	Interview, 2 questions (nightmares per week and dream enactment)	ON SSRI / SNRI: ↑nightmare frequency* ↑dream enactment*
D. Six clinical studies reporting on dream data as an additional study outcome (using one scale or structured question or an unstructured interview, but neither REM sleep awakening nor a daily diary)						
1982 Becker & Dufresne[63]	24	0	nd	Bupropion vs. tricyclic or tetracyclic ADs	Interview, 1 scale (vivid imagery and dreams)	ON bupropion ↑vivid imagery and dreams vs. ON tricyclic or tetracyclic ADs (50% vs. 8% of patients)
1982 Bialos et al.[64]	10	0	nd	Amitryptiline	Unstructured interview	WDRA: during the first few weeks "dream disturbance" in 8/10 patients

Table 1 (*continued*)

	Pat.	Healt.	Fem.	AD	Methods	Results
1987 Wiegand et al.[65]	10	0	8	Trimipramine	Unstructured interview	ON: 6 of 10 patients "very lively, intense dreams"; emotional content neutral to positive; frequently themes from childhood
1989 Guelfi et al.[66]	265	0	181	Tianeptine, amitriptyline	Side-effect check list, 1 question (insomnia or nightmares)	ON tianeptine ↑"insomnia or nightmares" vs. ON amitriptyline*
1993 Besançon et al.[67]	65	0	43	Mianserine, fluoxetine	Interview, 1 question (increased dream activity)	ON mianserine ↓"dream activity" vs. ON fluoxetine*
2009 Montgomery et al.[68]	1724	0	nd	Desvenlafaxine, placebo	Unstructured interview	WDRA: ↑"abnormal dreams" after desvenlafaxine vs. after placebo (2.6% vs. 0.5% of patients)

AD: antidepressant; DRF: dream recall frequency; Fem.: females; Healt.: healthy volunteers; nd: no data; ns: not significant; ON: AD intake phase; Pat.: patients; PRE: pre phase without AD; REM: rapid eye movement; VAS: visual analogue scale; WDRA: phase of AD withdrawal; *: $p \leq 0.05$; no star (results column): difference or change, statistically not tested.

Impact of different ADs on dreaming

Tricyclic ADs

Tricyclic ADs may reduce DRF (trimipramine significantly,[39] imipramine significantly[44] and statistically not tested[52]). Withdrawal from tricyclic ADs may increase DRF (imipramine, statistically not tested[52]). Tricyclic ADs may induce more pleasant dreams (trimipramine significantly[39] and statistically not tested,[65] three different tricyclic ADs significantly[46]) and less anxiety in dreams (imipramine significantly[45]). Few other dream content scales showed significant changes on tricyclic ADs, i.e., increased hostility per word,[44] increased heterosexuality,[45] and fewer family members as compared to friends and strangers.[46] During withdrawal from tricyclic ADs, seven cases developed either nightmares[71,74,75,79] or vivid dreaming.[73] This phenomenon does not only happen after high dosages in the range of acute intoxication[71] or chronic abuse,[73] but also with a daily intake of 150–300 mg imipramine.[75,79]

SSRIs and SNRIs

Fluoxetine and the 5-HT_{2A} receptor antagonist nefazodone significantly reduced DRF in a group of 21 patients; however, four of the 13 study patients receiving fluoxetine showed an increase of DRF (statistically not tested).[24] Under these two ADs dream content was "very similar to baseline", though five out of 18 content rating scales in this study showed a significant decrease (reduced vividness, number of scenes, presence of others, body presence, and sexual content).[24] A higher "dream activity" was found on fluoxetine as compared to the tetracyclic AD mianserine.[67] Fluoxetine alone produced nightmares ($n = 5$[81,84,91]) and an intensification of dreaming (negative intensification $n = 1$,[82] not further specified $n = 1$,[83] positive $n = 4$[80]). RBD or RBD-like symptoms have been developed or perhaps unmasked in three depressive cases during a newly established therapy with fluoxetine[91] or another SSRI/SNRI (paroxetine[89] and venlafaxine[86]).

Fluvoxamine and paroxetine reduced DRF and increased visual vividness, emotional intensity, and meaningfulness.[57] During withdrawal from these two SSRIs, increases in memorability, visual vividness, and amount of sound were found.[57] Withdrawal from fluvoxamine but not from paroxetine increased word count and bizarreness.[57] Withdrawal from desvenlafaxine resulted in an increase of "abnormal dreams" (more than five times the placebo rate; statistically not tested).[68] In depressive patients with features suggestive of RBD, a change from treatment with SSRIs/SNRIs to bupropion or to no AD reduced nightmare frequency and dream enactment.[61]

Phenelzine

Treatment with phenelzine reduced DRF[19] and was associated with absolutely no dream report during a total of 160 nights of total REM sleep suppression.[53] Withdrawal from phenelzine resulted in "frequently reported dreams, many of which were frightening" (statistically not tested).[53] Five participants of case studies also reported nightmares during withdrawal of phenelzine.[72,76,77] In one of these cases disappearance of nightmares is documented 24 h after resumption of phenelzine therapy.[77]

Possible links between clinical improvement under ADs and change in dream characteristics

Tricyclic ADs

Four studies exclusively using tricyclic ADs[39,45,46,65] have found an improvement both of depressive clinical symptoms and of dream quality. Improved clinical dimensions were: depressive symptomatology, sleep disturbances, anxiety, and restlessness (all[39]), Beck depression inventory,[45] and Hamilton depression rating scale (statistically not tested[46,65]). Improved dream quality was found in two dimensions: more pleasant emotions (significantly,[39,46] statistically not tested[65]) and reduced anxiety.[45] Only one study of this review (1179 patients taking trimipramine) calculated correlations between clinical improvement and dream emotion improvement, which were highly significant.[39]

Fluoxetine

Positive dream intensification under fluoxetine appeared even before the clinical improvement of depressive symptoms in four cases.[80] However, developing nightmares[81,84,91] or a negative intensification of dreaming[82] on fluoxetine does not impede a clinical improvement of depressive symptoms; four of six cases on fluoxetine[81,82,84,91] still improved clinically in spite of experiencing bad dream quality.

Phenelzine

A clinical improvement on phenelzine (Hamilton depression rating scale significantly improved[19] and "behaviour … markedly improved" without reporting a level of significance[53]) was paralleled by a very high degree of dream suppression.[19,53] Withdrawal from phenelzine resulted in explicit nightmares[72,76,77] as well as in "frequently reported dreams, many of which were frightening" (statistically not tested).[53]

ADs effects on dreaming in healthy volunteers

Imipramine showed reduced DRF in two studies (significantly,[44] statistically not tested[52]). In another study amitriptyline[43] showed no effect on dreaming. Fluvoxamine and paroxetine[57] also reduced DRF and increased responses in some content scales (for

Table 2
Twenty-five case studies reporting dream data under antidepressants in depressive patients ($n = 32$) and in healthy volunteers ($n = 3$).

	Pat.	Healt.	Fem.	AD	ON antidepressant treatment					WDRA from antidepressant	
					Nightmares or negative intensification of dreaming	Emotionally undetermined intensification of dreaming	Positive intensification of dreaming	Other effect	RBD (like) symptoms	Nightmares or negative intensification of dreaming	Emotionally undetermined intensification of dreaming
1965 Le Gassicke[69]	1	0	0	Tranylcypromine (addiction)						1	
1967 Cramer & Ohlmeier[70]	1	0	0	Tranylcypromine (addiction)						1	
1969 Lewis & Oswald[71]	3	0	3	Amitriptyline, nortriptyline, imipramine (intoxications)						3	
1970 Akindele et al.[72]	1	2	1	Phenelzine						2	1
1978 Brown et al.[73]	1	0	0	Desipramine (abuse)							1
1981 Boisvert & Chouinard[74]	1	0	1	Imipramine						1	
1983 Dilsaver et al.[75]	1	0	0	Imipramine						1	
1983 Joyce & Walshe[76]	2	0	1	Phenelzine						2	
1983 Palladino[77]	1	0	1	Phenelzine						1	
1986 Menza[78]	1	0	0	Trazodone						1	
1990 Kantor[79]	1	0	1	Tricyclics						1	
1991 Markowitz[80]	4	0	3	Fluoxetine			4				
1992 Lebegue[81]	1	0	0	Fluoxetine	1						
1994 Balon[82]	1	0	1	Fluoxetine	1						
1994 Pace-Schott et al.[83]	0	1	nd	Fluoxetine		1					
1995 Lepkifker et al.[84]	3	0	1	Fluoxetine	3						
1996 Balon[85]	1	0	1	Bupropion	1						
1996 Schuttle[86]	1	0	0	Venlafaxine	1				1		
2000 Zullino & Riquier[87]	1	0	1	Venlafaxine	1						
2006 Mathews et al.[88]	1	0	0	Mirtazapine	1						
2007 Parish[89]	1	0	0	Paroxetine	1				1		
2009 Applebee et al.[91]	1	0	0	Fluoxetine	1				1		
2009 Dang et al.[90]	1	0	0	Mirtazapine	1						
2010 Felthous et al.[92]	1	0	0	Mirtazapine vs. bupropion	1				1		
2010 Ishida et al.[93]	1	0	1	Sertraline				Disappearance of nightmares			
	32	3	16		13	1	4	1	4	14	2

AD: antidepressant; Fem.: females; Healt.: healthy volunteers; nd: no data; ON: AD intake phase; Pat.: patients; RBD: REM sleep behavior disorder; VAS: visual analogue scale; WDRA: phase of AD withdrawal.

details see Clinical findings, B). Withdrawal of phenelzine produced excessive, vivid and sometimes frightening dreaming (statistically not tested[72]).

Discussion

The reviewed studies document a clear effect of ADs on dream recall and dream content. The major finding is a decrease of DRF under ADs, a rather consistent effect in tricyclic ADs[39,44,52] and phenelzine,[19,53] less consistently documented also for SSRIs/SNRIs.[24,57] ADs reduced DRF both in depressed patients[14,19,33,45] and in normal volunteers.[35,44,49] Administration of SSRIs/SNRIs may increase frequency of nightmares.[61] Withdrawal of tricyclic ADs,[52,64] phenelzine,[53] and desvenlafaxine[68] may increase DRF.

Dream quality is positively influenced by tricyclic ADs, which can induce more positive dream emotions (more pleasantness, less anxiety),[39,45,46,65] correlating with clinical improvement.[39] Withdrawal from tricyclic ADs may cause nightmares,[71,74,75,79] vivid dreaming[73] or "dream disturbance".[64] Also withdrawal of the monoamine oxidase inhibitors phenelzine[53,72,76,77] and tranylcypromine[69,70] may cause nightmares. The reviewed evidence on dream quality under SSRIs/SNRIs is less consistent, different effects are documented. Both treatment and withdrawal of fluvoxamine and paroxetine intensified dreaming in some quality scales.[57] On the other hand fluoxetine (together with nefazodone) reduced responses in some content scales.[24] Fluoxetine produced a higher "dream activity" as compared to mianserine.[67] Fluoxetine alone intensified dreams, both negatively and positively.[80–84,91] SSRIs/SNRIs unmask or perhaps induce RBD (-like) symptoms.[61,86,89,91] Taken together, intake and even more withdrawal of SSRIs/SNRIs seem to intensify dreaming, which may be experienced in different ways; a potential to cause nightmares has to be taken into account.

Subclinical or full symptom RBD is associated with and probably can be induced by serotonergic and by tricyclic ADs,[96–100] strong evidence for drug-induced RBD has been reported for clomipramine.[101] Vivid dreaming and nightmares have been described during treatment[102] and withdrawal of serotonin reuptake inhibitors,[103] not only in depression.[96] A study on obsessive-compulsive disorder used relatively high dosages of citalopram (up to 60 mg daily), 6% of the patients complained of "increased dreaming".[104] A couple of the reviewed studies documented AD administration associated signs of RBD by polysomnography: under paroxetine increased submental muscle activity and vocalizations during REM sleep[89]; under both paroxetine and fluvoxamine significantly increased eyelid movements in REM sleep[57]; under venlafaxine episodes of elevated leg EMG in otherwise clear REM sleep[86]; and under fluoxetine persistent chin muscle tone.[91] In a series of 1235 patients from a psychiatric outpatient clinic in Hong Kong, 5% of the patients taking SSRIs were found to report RBD-like symptoms (the OR of having an active RBD-like disorder was 3.7, 95% CI = 1.6 to 8.7, $p < 0.05$).[105] The present review provides further evidence that there is probably a not dosage dependent effect in ADs, primarily in SSRIs,[105] to induce a continuum from intensification of dreaming, to nightmares, sometimes up to even RBD.[42,106]

AD effects on dreaming are frequently accompanied by changes in polysomnographic parameters.[107] During acute intoxication with tricyclic ADs, an initially total REM sleep suppression has been described.[71] After one to four weeks, a strong REM sleep rebound (up to a peak of 45% of total sleep time) and a reduction of non-REM sleep followed, accompanied by vivid, heavily unpleasant dreaming.[71] Comparable courses of sleep parameters and dreaming have been described during and after intake of both phenelzine[53,72] and tranylcypromine.[69] Acute withdrawal from tranylcypromine overuse caused terrifying nightmares and a REM sleep rebound of up to 76% of total sleep time.[69] Though phenelzine treatment may suppress REM sleep completely,[19,53] this is not necessarily accompanied by dream suppression.[19] Interestingly, the tricyclic AD trimipramine has atypically little impact on REM sleep parameters,[36] but still shows a clear DRF reduction.[39] Evidence for REM sleep suppression during SSRI treatment followed by REM rebound phenomena during withdrawal is provided by the finding of significantly longer REM latency during treatment compared with the pre phase without SSRI and greater eyelid movement density in REM during withdrawal compared with both the pre and the treatment phases.[57] Intensification of dreaming during acute discontinuation of SSRIs seems to be related to REM rebound phenomena.[57] But the REM sleep suppressive effect of SSRI treatment does not provide a convincing explanation for the phenomenon of intensified dreaming under SSRIs.[42,57]

Considering the neurochemical basis of the wake-sleep-cycle,[108] cholinergic pedunculopontine tegmental neurons act as REM-on cells, serotonergic dorsal raphe nucleus and noradrenergic locus coeruleus neurons act as REM-off cells.[109] Aminergic tuberomammillary nucleus, locus coeruleus, and dorsal raphe nucleus are almost completely silent during REM sleep, which leads to a desinhibition of REM-active cholinergic laterodorsal tegmental and pedunculopontine areas.[110] According to the reciprocal interaction model, the brain during REM sleep has been considered aminergically demodulated and, reciprocally, cholinergically hypermodulated.[109,111] REM sleep abnormalities of depression, consisting primarily in reduced REM latency and increased REM density,[35] are relieved by drugs which enhance aminergic efficacy and suppress the cholinergic system.[111] Also in healthy subjects ADs significantly increase REM latency[112] and decrease REM sleep.[112,113]

This review showed that ADs reduce DRF in healthy subjects[44,52,57] and in depressed patients[19,24,39,53]; the drug-naïve state of the latter is characterized by already low DRF[25] and contrasting high REM sleep amounts.[35] As REM sleep reduction under ADs may be attributed to aminergic effects, this property of ADs may also cause the parallel decrease of DRF. The anticholinergic potential of tricyclic ADs might further enhance this effect. But effects other than REM sleep suppression and aminergic/anticholinergic pharmacology seem to be involved in this reduction of DRF during AD intake. The structurally atypical nefazodone has low level noradrenergic, serotoninergic and dopaminergic potentials, no anticholinergic properties[36] as well as little impact on REM sleep,[36] but still showed a clear reduction in DRF.[24] In contrast to tricyclics, SSRIs have little or no anticholinergic capacities, which could explain the subjectively both positive and negative experienced intensification of the quantitatively reduced dreaming under SSRIs.

More difficult to explain remains the clear positive effect of tricyclic ADs on dream content; a positive anticholinergic influence on dream quality may be supposed. Such an anticholinergic effect on dream content is not necessarily or only due to REM sleep effects. The anticholinergic, tricyclic trimipramine has very little impact on REM sleep parameters[36] but still has the capacities to improve dream emotions[39,65] and to reduce DRF.[39] Anticholinergic agents may cause hallucinations,[114] but these are rarely experienced as emotionally positive and cannot serve as a model to explain the emotionally positive toning of dreams by tricyclic ADs. Another possible explanation would be an indirect influence of AD improved daytime mood on dream content; but this theory would also have to explain why this would be reached more consistently with tricyclic ADs than with SSRIs. However, the reviewed literature documents relatively consistently a parallel improvement of clinical symptoms and dream quality in depressive patients under tricyclic ADs, while such a parallel improvement seems much less predictable under SSRIs.

Independently of the substance classes, there is a potential to develop nightmares in the acute phase both during implementation and even more so after stopping of an AD treatment. Administration of SSRIs seems to have a higher potential to cause nightmares than intake of tricyclic ADs, which might be explained by the activating properties of SSRIs.

This systematic review could identify 21 clinical studies and 25 case studies in a period of 60 years. This considerably low number of publications reflects little scientific interest in effects of ADs on dreaming. This is further highlighted by the facts that only four studies systematically used REM sleep awakenings (most recently in 1978) and that since 2000 only five clinical studies have been published. Protocols and quality of the studies show a high heterogeneity, little placebo control has been applied, and dream parameters have been measured mainly remote from dreaming time. The clinical studies often performed no statistical comparisons or reported descriptive data only. Also methodological limitations have to be considered.[111,115–117] E.g., the very elaborate study by Hartmann and Cravens[43,47,48] could not find a single significant change in dream parameters, though it investigated amitriptyline, a substance with sedative and amnesic effects and strong anticholinergic properties,[118] measured dream outcome by home sleep logs for 60 nights and by induced awakenings during two sleep laboratory nights, and used a number of Hall & Van-de-Castle as well as other dream scales. This scarcity of data could be interpreted as the documentation of an absence of a considerable effect of ADs on dreaming. But contrasting the 25 clinical studies retrieved to the tens of thousands of published studies on other AD effects, it seems reasonable to assume that both more and more sophisticated studies on dreaming under ADs could document

further effects. However, considering these quantitative, qualitative and probably also methodological limitations, any generalization beyond the statement of very little published data has to be deduced cautiously.

Also the most elaborate study in this set, performed by Pace-Schott et al.,[57] shows methodological limitations. According to the methods section, the pathognomonic symptoms for diagnosis establishment of "nightmare disorder", i.e., dream mentation of fear or anxiety, anger, and sadness (ICSD-R [international classification of sleep disorders, revised] 1997, ICSD-II 2005), were investigated, as well as other, positive emotions like joy/elation and affection/erotic. But the results section reports only an intensification of a combined score of all emotions, differentiating neither between these enumerated categories nor between any negative or positive emotions at all. This paper extensively documents subjective dream intensification on fluvoxamine and paroxetine, and also during withdrawal from these two SSRIs. But it does not allow for information, if this increase of subjective dream intensity was a positive or negative experienced dream mentation, and whether this phenomenon has a potential to induce bad dreams or nightmares. According to the literature, such an effect is highly probable to occur at least occasionally while taking or stopping SSRIs, respectively.

AD impact on sleep parameters, measured by polysomnography and by psychometric batteries, has been studied and published widely. But this routine mapping of AD effects has not been extended to AD effects on dreaming. It seems that pharmaceutical studies produce more data on dreaming and nightmares than what up to now has been published, at least in a – for dream research – accessible manner. For example, the prescribing information of the combined SSRI/SNRI Cymbalta™ (Duloxetine) mentions that 2% of patients taking this substance reported "abnormal dreams – including nightmares". This effect was double as high as the rate under placebo.[119] Our review could not find a scientific publication that would allow for more detailed information about this observed phenomenon.

Conclusions

Considering treatment process, the various classes of ADs have a different potential to reduce DRF, which is accompanied by a spectrum of impact on dream content. Especially in psychotherapy and psychoanalytic dream work in depressed patients, a more personalized approach toward AD pharmacotherapy[120] may be implemented, according to patients' needs. Pharmacological effects of ADs, as well as of other psychotropic drugs, on dreaming are theoretically and clinically relevant. They should be considered both targets of scientific interest and results worthy of being published accessibly.

Practice points

Both antidepressant use and withdrawal can induce nightmares and other negative as well as positive changes in dreaming. Evidence based clinical practice should include awareness of these effects and may implement them intentionally:

1) Tricyclic antidepressants have a potential to induce more positive dream emotions;
2) SSRIs have a dream intensifying effect and may elicit more dream material;
3) Phenelzine may virtually suppress dreaming.

Research agenda

Studies on antidepressants should:

1) At minimum, monitor the occurrence of nightmares;
2) Investigate any form of positively or negatively experienced quantitative and qualitative changes in dreaming in a structured, systematic way, both during antidepressant administration and during withdrawal;
3) Publish these data.

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