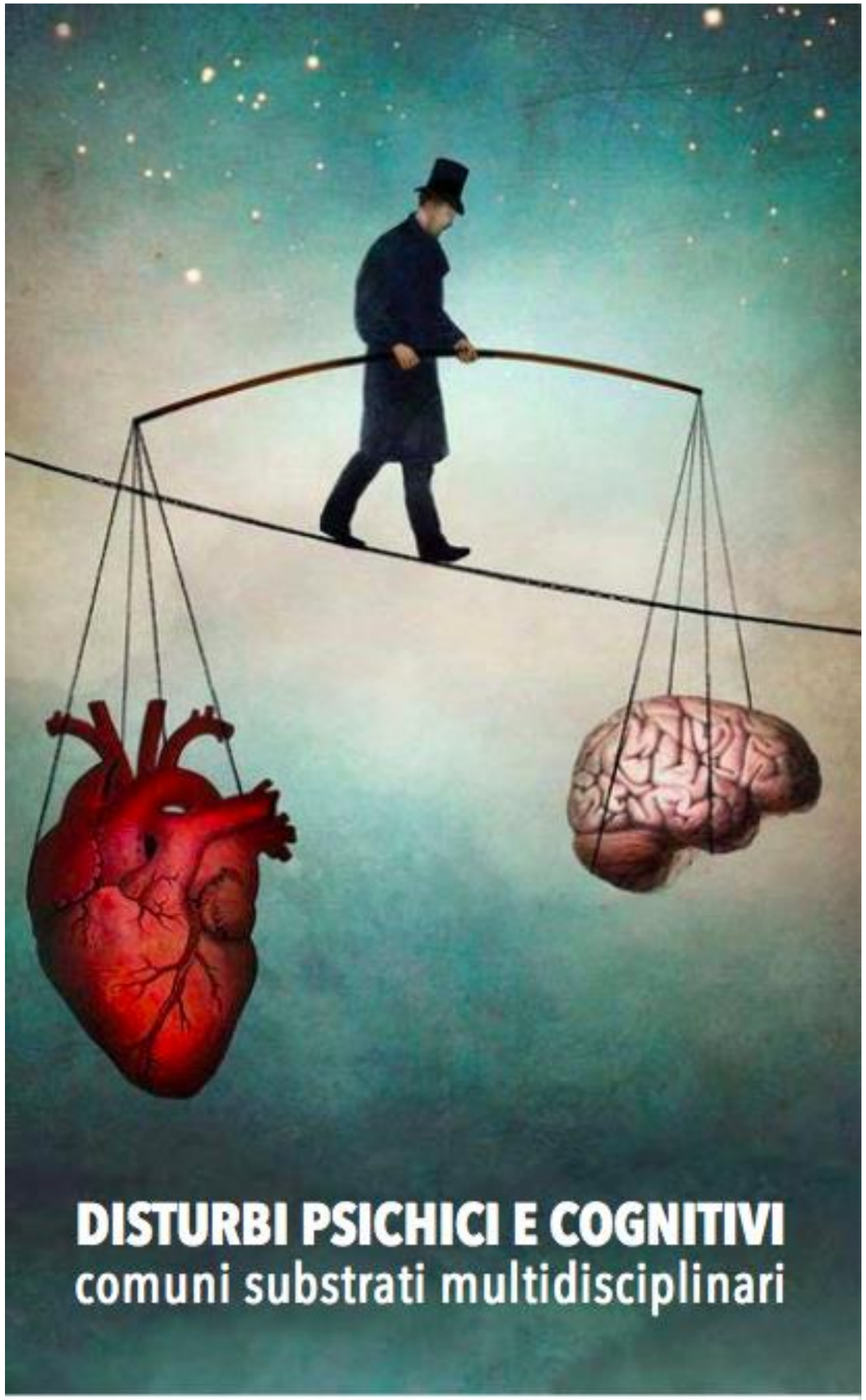
Depressione e Malattia Cerebrovascolare

Alba Caruso
U.O. NEUROLOGIA
Ospedale S. Stefano *Prato*



LE CURE ED I TRATTAMENTI

Bidirectional relationship between depression and stroke

- Depression is an independent risk factor for stroke and stroke mortality
- Stroke as causes of depression (Post Stroke Depression PSD)

- Vascular depression

Common pathophysiology

Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study

Martin J O'Donnell, Denis Xavier, Lisheng Liu, Hongye Zhang, Siu Lim Chin, Purnima Rao-Melacini, Sumathy Rangarajan, Shofiqul Islam, ankey, Antonio L Dans, Khalid Yu eimar, Xingyu Wang, Salim Yusu

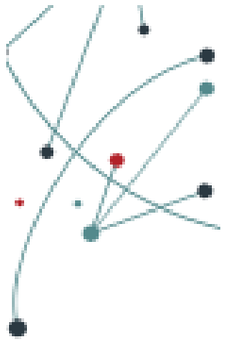
Lancet 2010; 376: 112–23

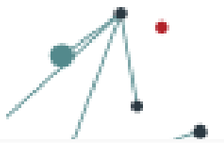
de is unknown, particularl

	Prevalence*			All stroke†		Ischaemic stroke†		Intracerebral haemorrhagic stroke	
	Control (n=3000)	Ischaemic stroke (n=2337)	Intracerebral haemorrhagic stroke (n=663)	Odds ratio (99% CI)	Population-attributable risk (99% CI)	Odds ratio (99% CI)	Population-attributable risk (99% CI)	Odds ratio (99% CI)	Population-attributable risk (99% CI)
Variable 1: hypertension									
A: self-reported history of hypertension	954/2996 (32%)	1277/2335 (55%)	399/662 (60%)	2·64 (2·26–3·08)	34·6% (30·4–39·1)	2·37 (2·00–2·79)	31·5% (26·7–36·7)	3·80 (2·96–4·78)	44·5% (37·2–52·0)
B: self-reported history of hypertension or blood pressure >160/90 mm Hg	1109/3000 (37%)	1550/2337 (66%)	551/663 (83%)	3·89 (3·33–4·54)	51·8% (47·7–55·8)	3·14 (2·67–3·71)	45·2% (40·3–50·0)	9·18 (6·80–12·39)	73·6% (67·0–79·3)
Variable 2: smoking status									
Current smoker‡	732/2994 (24%)	868/2333 (37%)	207/662 (31%)	2·09 (1·75–2·51)	18·9% (15·3–23·1)	2·32 (1·91–2·81)	21·4% (17·5–25·8)	1·45 (1·07–1·96)	9·5% (4·2–20·0)
Variable 3: waist-to-hip ratio									
T2 vs T1	989/2960 (33%)	768/2303 (33%)	266/655 (41%)	1·42 (1·18–1·71)	26·5% (18·8–36·0)§	1·34 (1·10–1·64)	26·0% (17·7–36·5)§	1·65 (1·22–2·23)	26·1% (14·1–43·3)§
T3 vs T1	984/2960 (33%)	987/2303 (43%)	231/655 (35%)	1·65 (1·36–1·99)	-	1·69 (1·38–2·07)	-	1·41 1·02–1·93)	-
Variable 4: diet risk score									
T2 vs T1	1064/2982 (36%)	842/2303 (37%)	271/658 (41%)	1·35 (1·12–1·61)	18·8% (11·2–29·7)§	1·29 (1·06–1·57)	17·3% (9·4–29·6)§	1·53 (1·13–2·08)	24·1% (11·9–42·7)§
T3 vs T1	904/2982 (30%)	807/2303 (35%)	221/658 (34%)	1·35 (1·11–1·64)	-	1·34 (1·09–1·65)	-	1·41 (1·01–1·97)	-
Variable 5: regular physical activity¶	362/2994 (12%)	193/2334 (8%)	45/662 (7%)	0·69 (0·53–0·90)	28·5% (14·5–48·5)	0·68 (0·51–0·91)	29·4% (14·5–50·5)	0·70 (0·44–1·13)	27·6% (6·8–66·6)
Variable 6: diabetes mellitus	350/2999 (12%)	495/2336 (21%)	68/662 (10%)	1·36 (1·10–1·68)	5·0% (2·6–9·5)	1·60 (1·29–1·99)	7·9% (5·1–12·3)	‖	‖
Variable 7: alcohol intake‡									
1–30 drinks per month	524/2989 (18%)	338/2326 (15%)	121/660 (18%)	0·90 (0·72–1·11)	3·8% (0·9–14·4)§	0·79 (0·63–1·00)	1·0% (0·0–83·8)§	1·52 (1·07–2·16)	14·6% (8·5–24·0)§
>30 drinks per month or binge drinker	324/2989 (11%)	383/2326 (16%)	108/660 (16%)	1·51 (1·18–1·92)	-	1·41 (1·09–1·82)	-	2·01 (1·35–2·99)	-
Variable 8: psychosocial factors									
A: psychosocial stress	440/2987 (15%)	465/2324 (20%)	124/654 (19%)	1·30 (1·06–1·60)	4·6% (2·1–9·6)	1·30 (1·04–1·62)	4·7% (2·0–10·2)	1·23 (0·89–1·69)	3·5% (0·7–16·3)
B: depression	424/2995 (14%)	489/2320 (21%)	100/645 (16%)	1·35 (1·10–1·66)	5·2% (2·7–9·8)	1·47 (1·19–1·83)	6·8% (3·9–11·4)	‖	‖
Variable 9: cardiac causes**	140/3000 (5%)	321/2337 (14%)	28/662 (4%)	2·38 (1·77–3·20)	6·7% (4·8–9·1)	2·74 (2·03–3·72)	8·5% (6·4–11·2)	‖	‖
Variable 10: ratio of ApoB to ApoA1††									
T2 vs T1	695/2091 (33%)	501/1698 (30%)	136/468 (29%)	1·13 (0·90–1·42)	24·9% (15·7–37·1)§	1·30 (1·01–1·67)	35·2% (25·5–46·3)§	‖	‖
T3 vs T1	696/2091 (33%)	825/1698 (49%)	165/468 (35%)	1·89 (1·49–2·40)	-	2·40 (1·86–3·11)	-	‖	‖

All models were adjusted for age, sex, and region. T=tertile. Apo=apolipoprotein. *Data were missing for some individuals: seven for self-reported history of hypertension, 11 for smoking status, 82 for waist-to-hip ratio, 57 for diet risk score, ten for physical activity, three for diabetes mellitus, 25 for alcohol intake, 35 for psychosocial stress, 40 for depression, one for cardiac causes, and 1743 for apolipoprotein concentrations; these individuals were excluded from the denominator in percentage calculations. †Individual risk-factor estimates for variables 1–9 are derived from the multivariable model, including all variables (1A and 2–9). For intracerebral haemorrhagic stroke, the multivariate model included variables 1A, 2–5, 7, and 8A. ‡Comparator for current smoker and alcohol intake is never or former. §For variables expressed in tertiles, population-attributable risk was calculated from T2 plus T3 versus T1. ¶For the protective factor of physical activity, population-attributable risks are provided for the group without this factor. ‖Odds ratio and population-attributable risk was not calculated because the variable was not significant in univariate analyses and so was excluded from multivariate analyses. **Includes atrial fibrillation or flutter, previous myocardial infarction, rheumatic valve disease, or prosthetic heart valve. ††Estimate derived from multivariable model, including all variables (1A and 2–10; n=4257).

Table 2: Risk of stroke associated with risk factors in the overall population (multivariate analyses)





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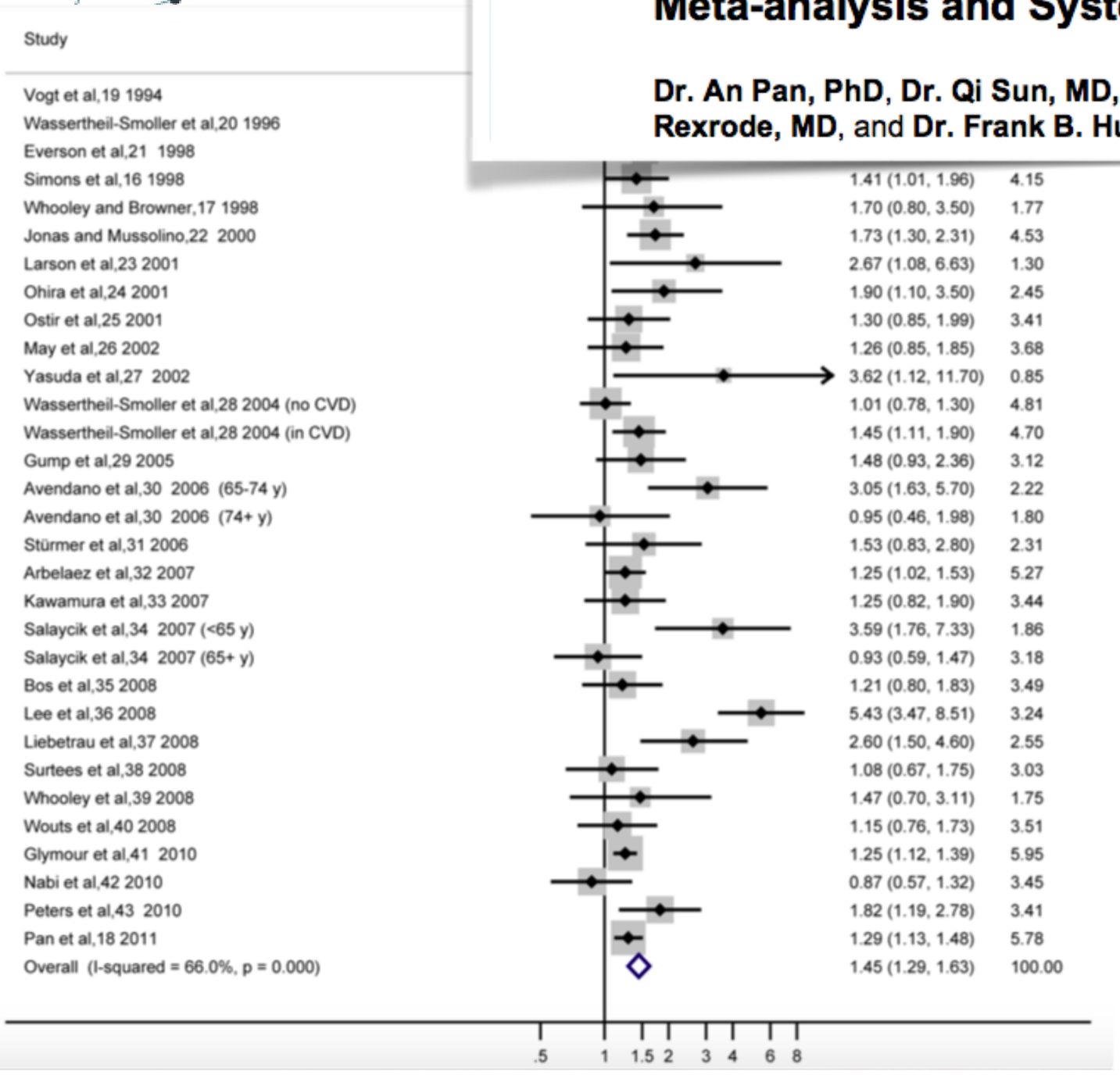
Depression and the Risk of Stroke Morbidity and Mortality: A Meta-analysis and Systematic Review

Dr. An Pan, PhD, Dr. Qi Sun, MD, ScD, Dr. Olivia I. Okereke, MD, SM, Dr. Kathryn M. Rexrode, MD, and **Dr. Frank B. Hu, MD, PhD**



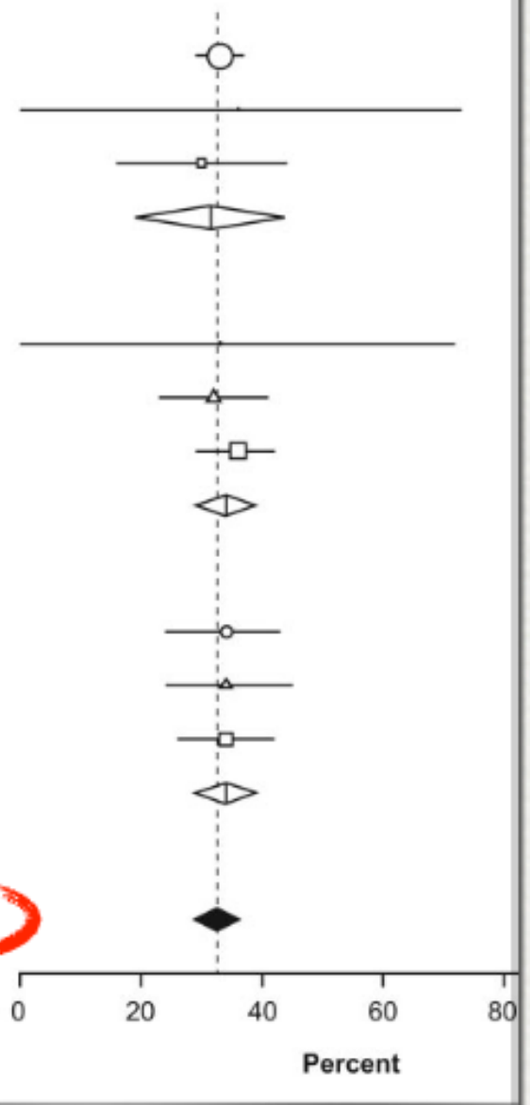
- neuroendocrine and immunological/inflammation effects
- poor health behaviors and obesity
- comorbidities (diabetes and hypertension)

Frequency of Depression After Stroke

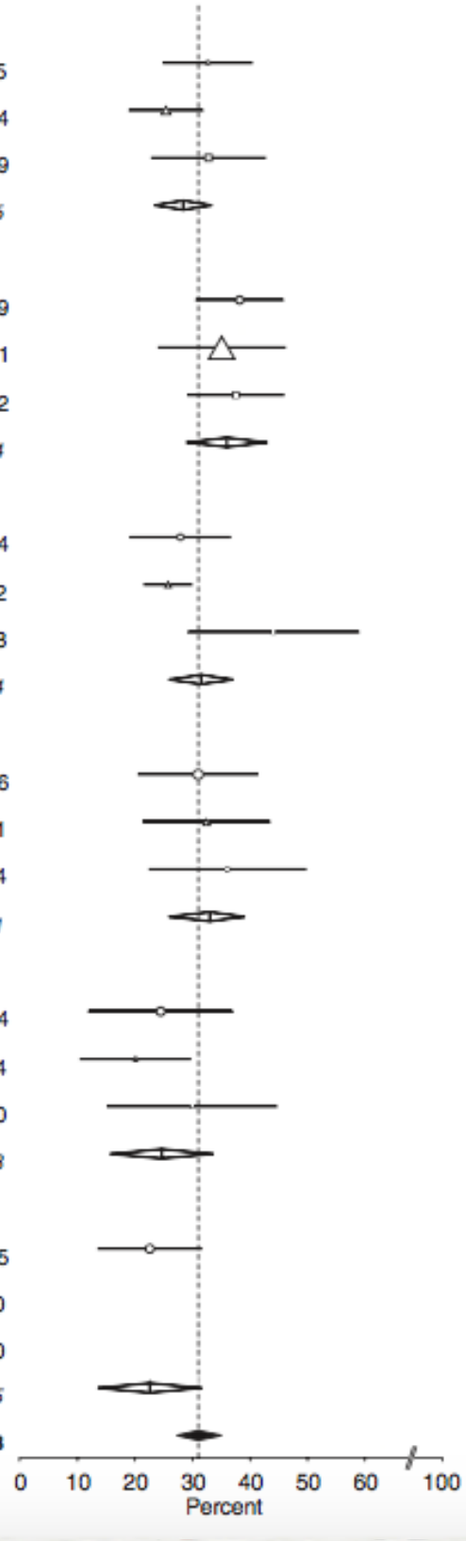
A Systematic Review of Ol

Maree L. Hackett, MA (Hons); Chaturangi Ya
Craig S. Anderson, PhD, F

Phase/study	*Proportional frequency (95% CI)*
Acute	
Population	33% (29% to 37%)
Hospital	36% (0% to 73%)
Rehabilitation	30% (16% to 44%)
Sub-total	*32% (19% to 44%)*
Medium-term	
Population	33% (0% to 72%)
Hospital	32% (23% to 41%)
Rehabilitation	36% (20% to 39%)
Sub-total	*34% (20% to 39%)*
Long-term	
Population	34% (24% to 43%)
Hospital	34% (24% to 45%)
Rehabilitation	34% (26% to 42%)
Sub-total	*34% (29% to 39%)*
Overall	***33% (29% to 36%)***



Time since stroke Recruitment type	Proportional frequency (95% CI)	N
0-1 month		
Population	33% (25% to 40%)	455
Hospital	25% (19% to 32%)	2,194
Rehabilitation	33% (23% to 43%)	1,639
Sub-total	*28% (23% to 33%)*	*4,466*
2-5 months		
Population	38% (31% to 46%)	1,699
Hospital	35% (24% to 46%)	15,581
Rehabilitation	38% (29% to 46%)	1,022
Sub-total	*36% (29% to 43%)*	*8,254*
6-9 months		
Population	28% (19% to 37%)	1,254
Hospital	26% (22% to 30%)	722
Rehabilitation	44% (29% to 59%)	248
Sub-total	*31% (26% to 37%)*	*2,224*
1 year		
Population	31% (21% to 41%)	2,946
Hospital	32% (21% to 43%)	801
Rehabilitation	36% (23% to 50%)	274
Sub-total	*33% (26% to 39%)*	*4,001*
2-4 years		
Population	24% (12% to 37%)	2,174
Hospital	20% (11% to 30%)	134
Rehabilitation	30% (15% to 45%)	100
Sub-total	*25% (16% to 33%)*	*2,408*
5 years		
Population	23% (14% to 31%)	1,845
Hospital		0
Rehabilitation		0
Sub-total	*23% (14% to 31%)*	*1,845*
Overall	**31% (28% to 35%)**	**25,488**



Maree L. Hackett[1,2]* and Kristen Pickles[1] 2014

Post Stroke Depression (**PSD**) depression state present after stroke regardless of the timin[illegible] symptoms onset

Depress
Due to Another Medic

Diagnostic Criteria

A. A prominent and persistent period of depressed mood or marke[illegible] or pleasure in all, or almost all, activities that predominates in t[illegible]

B. There is evidence from the history, physical examination, or lab[illegible] disturbance is the direct pathophysiological consequence of [illegible] tion.

C. The disturbance is not better explained by another mental dis[illegible] disorder, with depressed mood, in which the stressor is a seric[illegible]

D. The disturbance does not occur exclusively during the course [illegible]

E. The disturbance causes clinically significant distress or impair[illegible] tional, or other important areas of functioning.

Coding note: The ICD-9-CM code for depressive disorder due to [illegible] tion is **293.83,** which is assigned regardless of the specifier. The ICD-10-CM code depends on the specifier (see below).

Depressive Disorder Due to Stroke

Specify if:

(F06.31) With depressive features: Full criteria are not met for a major depressive episode.

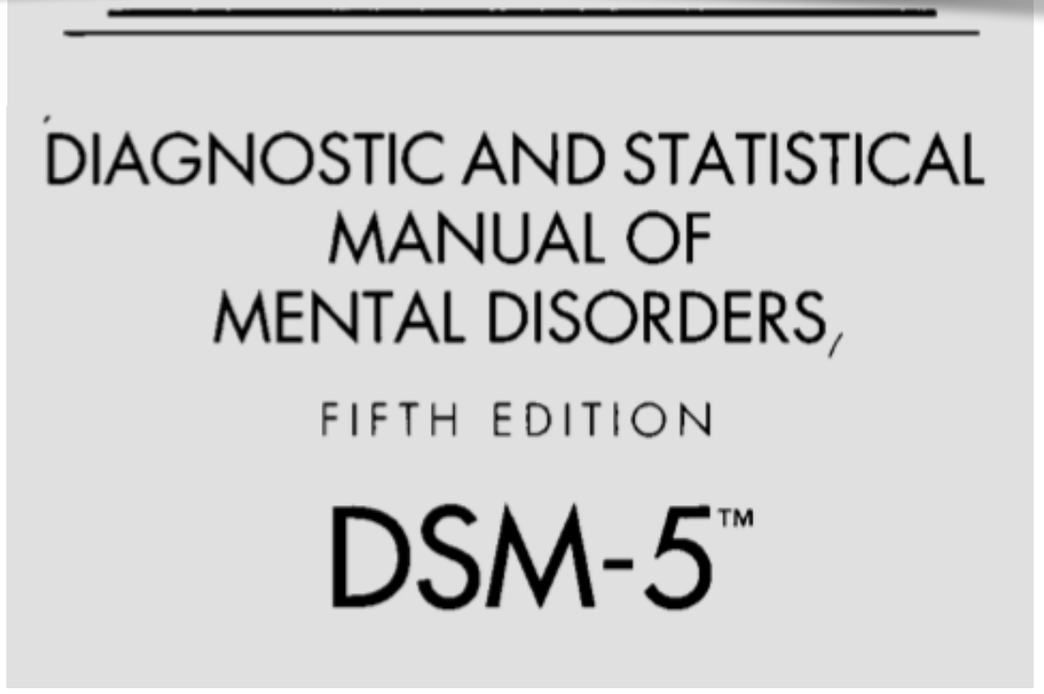
(F06.32) With major depressive–like episode: Full criteria are met (except Criterion C) for a major depressive episode.

(F06.34) With mixed features: Symptoms of mania or hypomania are also present but do not predominate in the clinical picture.

Coding note: Include the name of the other medical condition in the name of the mental disorder (e.g., 293.83 [F06.31] depressive disorder due to hypothyroidism, with depressive features). The other medical condition should also be coded and listed separately immediately before the depressive disorder due to the medical condition (e.g., 244.9 [E03.9] hypothyroidism; 293.83 [F06.31] depressive disorder due to hypothyroidism, with depressive features).

DSM-5: MDD

- Core features: 1) Depressed mood *or* 2) loss of interest;
- AND ≥ 5 associated symptoms for 2+ weeks:
  - **Depressed mood** most of the day;
  - Markedly diminished interest or **anhedonia**;
  - Significant **weight loss** (not intestinally trying);
  - **Insomnia** (typical) or **hypersomnia** (atypical)
  - **Psychomotor** agitation or retardation;
  - **Fatigue** or anergia;
  - Feelings of **worthlessness** or excessive / inappropriate **guilt**;
  - Diminished ability to think, **concentrate**, make decisions;
  - Recurrent thoughts of death or **suicidal ideation.**



Post Stroke Depression (PSD)

Negatively affects:

- functional outcome
- response to rehabilitation
- quality of life

Razmara, A.*J Stroke Cerebrovsc Dis* 2017

Increased mortality

- HR of 1.56 (95% CI 0.49-5.02, NS) at the ages between 25 and 74 years,
- **HR 2.28** (95% CI 1.79-2.90) for patients aged 65-74 years

Increased mortality in PSD patients might be the result of cardiovascular mortality: decreased heart rate variability, caused by the alteration of autonomic functions (Robinson et al., 2008).

PSD - Historical perspective

Isolated studies in the 1960s: “empathic understanding” (emotional reaction to the loss of independence).

In 1977 Folstein et al. conducted a study comparing the prevalence of mood disorders in patients with stroke or orthopedic problems which all presented comparable functional disability. They observed that patients with stroke exhibited a far greater frequency of depression than orthopedic patients, and concluded that mood disorders would be a complication of stroke that was linked not only to the degree of functional disability.

In the 1980’s by Robert Robinson’s group (University of Iowa): “…lesion location hypothesis: depression severity associated with lesions of left frontal lobe, stronger in the first 6 months after stroke …”

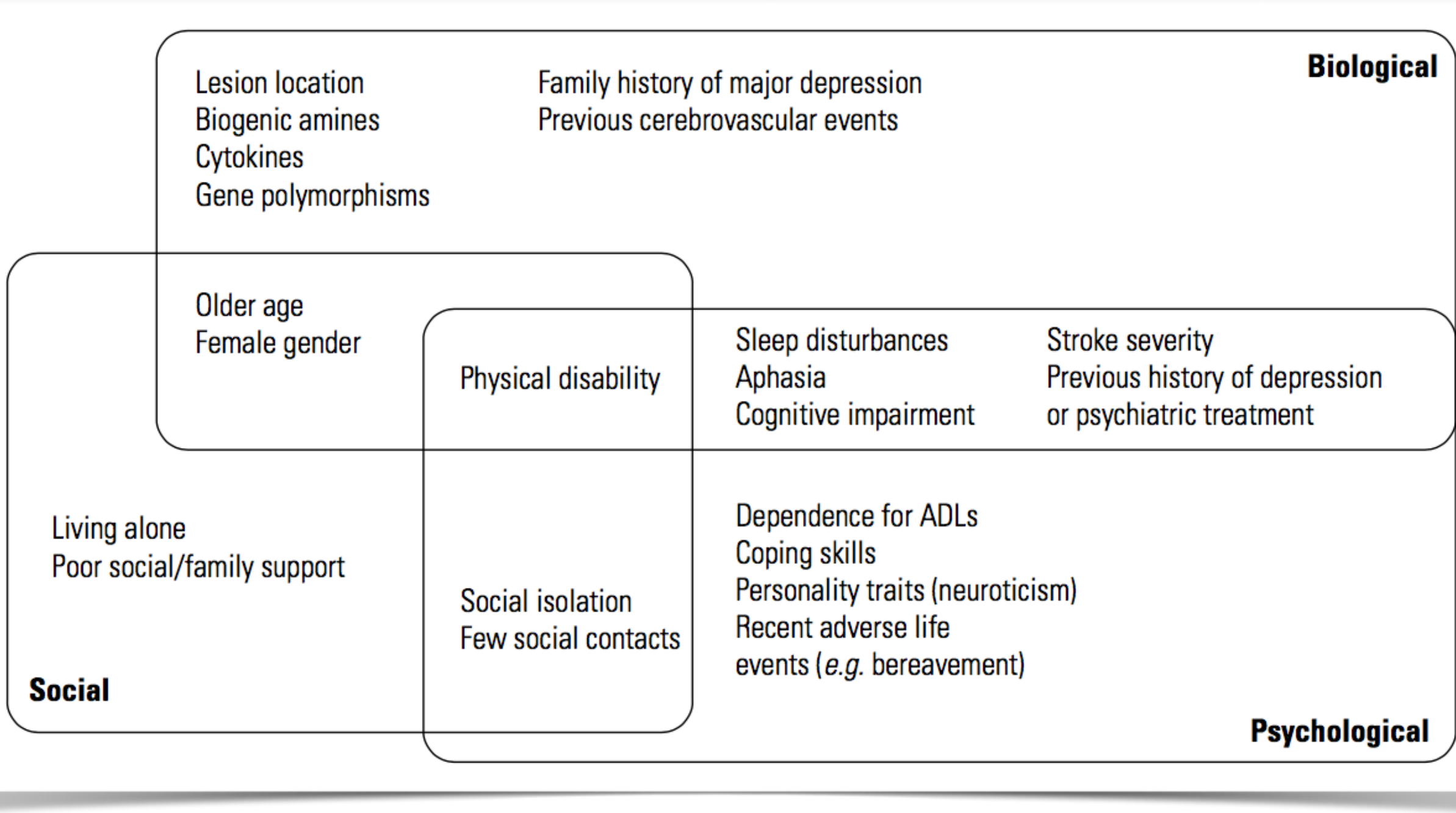
In the 1990s Guido Gainotti’s group (Catholic University of Rome), “… depressive syndromes associated with stroke may not be “true” depressions, but a completely different category from Major Depressive Disorder (MDD) that would be associated with the patients’ adjustment to changes in their living conditions…”

Biological and psychological hypothesis

Biological causation		Psychological causation	
Evidence		Evidence	
For	Against	For	Against
Higher frequency of depression in stroke *versus* other similarly disabling medical illness Temporal relationship between stroke and onset of depression Specific lesions associated with PSD PSD may occur in the context of silent infarcts	Finding not consistently replicated Temporal relationship between psychological stressors (*e.g.* bereavement) and depression Finding not consistently replicated -	PSD symptom profile is not specific and may be a form of "functional" depression Temporal relationship between psychological stressors (*e.g.* bereavement) and depression Risk factors unrelated with stroke predicts occurrence of depression (*e.g.* family history of depression) Disability severity is the most consistent risk factor for PSD and psychosocial factors become increasingly important in later onset PSD	"Functional" depression may have biological underpinnings Temporal relationship between stroke and onset of depression These risk factors may reflect biological predisposition (*e.g.* genetic causes) -
Explanatory theories		**Explanatory theories**	
Lesion location theory: PSD may be related to the location of the lesions, disturbing specific areas of the brain (*e.g.* left frontal lobes, hippocampus, basal ganglia) Biogenic amines theory: PSD may be related to disruption of monoamines circuitry, through direct or indirect mechanisms Inflammatory cytokines theory: PSD may be related to the production of "depressogenic" cytokines by the inflammatory response to ischemia Genetic polymorphisms theory: PSD may be related to genetic predisposition, especially in the serotoninergic system		Patients with stroke experience a traumatic event that undermines their physical and mental integrity, their autonomy and self-esteem as well as their social lives. Psychological coping mechanisms, as well as premorbid personality, are responsible for the development of PSD	

Pedroso VSP et al. / Arch Clin Psychiatry. 2015;42(1):18-24

A Biopsychosocial Model of PSD



Pedroso VSP et al. / Arch Clin Psychiatry. 2015;42(1):18-24

Pathogenetic mechanisms

Monoaminergic hypothesis: interruption induced by the ischaemic lesion of the amine-containing axons ascending from the brainstem to the left cerebral cortex. Reduced synthesis of 5-HT and of norepinephrine (NE) in limbic areas of frontal and temporal lobes and basal ganglia . *(Robinson et al., 1984; Santos et al., 2009; Terroni et al., 2011; meta-analysis by Narushima et al., 2003)*

Glutamate-mediated excitotoxicity hypothesis *(Sanacora et al., 2012)*

Neuroinflammatory response, based on the activation of microglia and astrocytes and up-regulation of pro- inflammatory cytokines (IL-1 , IL-6, IL-18 and TNF-). *(Ferrari and Villa, 2017)*

Pro-inflammatory cytokines stimulate the ***hypothalamic-pituitary-adrenal axis*** to release glucocorticoid hormones *(Szczudlik et al., 2004).*

Neuronal plasticity (Impairment of adaptive response of brain to ischaemia) *(Ferrari and Villa, 2017; Masi and Brovedani, 2011)*

Decreased levels of ***BDNF*** **- Brain Derived Neurotrophic Factor** *(Yang et al.2011)*

Vascular factors, such as the white matter lesions could interrupt monoaminergic projections from midbrain and brainstem. *(Taylor, W.D. 2013)*

Mitochondrial energy metabolism *(Villa et al., 2013)*

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The Vascular Depression Hypothesis: Mechanisms Linking Vascular Disease with Depression

Warren D. Taylor, MD, MHSc[1], **Howard J. Aizenstein, MD, PhD**[2], and **George S. Alexopoulos, MD**[3]

Late-Life Depression

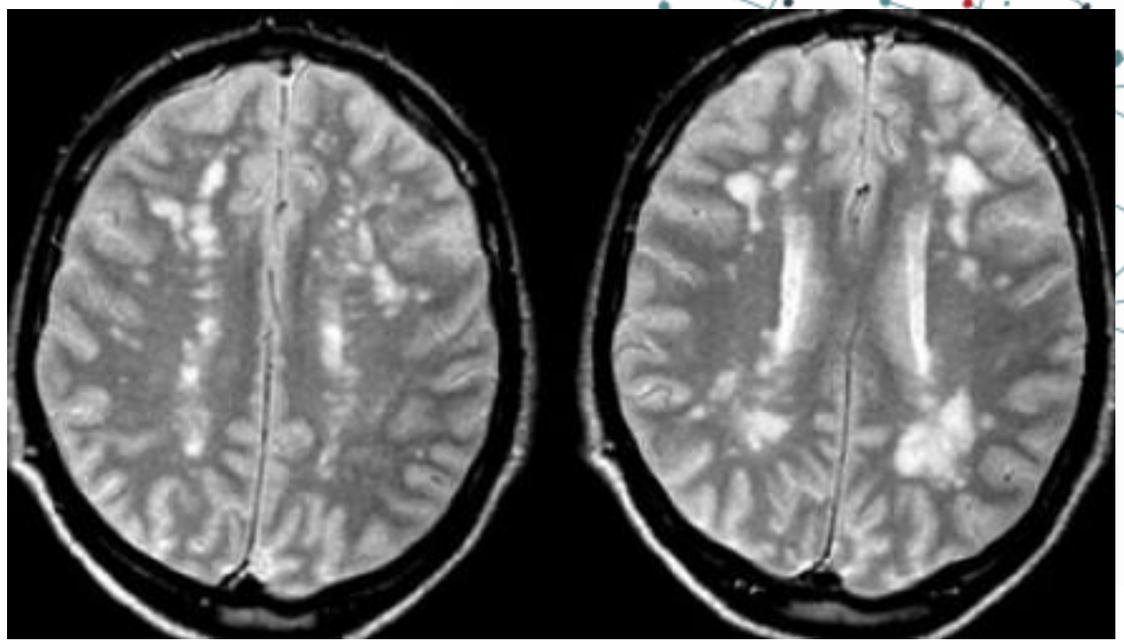
Presence of vascular risk factors

Clinical presentation

- cognitive deficits
- psychomotor retardation
- lack of insight
- disability disproportional to the depression severity

Depression-Executive Dysfunction (**DED**) Syndrome

White Matter Lesions (WMLs) white matter hyperintensities (WMH) on T2-weighted or fluid attenuated inversion recovery (FLAIR) MRI.



Depression develops for abnormalities in the fronto-limbic and fronto-striatal neural circuits, which are critical to both mood regulation and to executive functions

(Tekin and Cummings, 2002)

Prefrontal processes are supported by multiple neurotransmitters, including dopamine, norepinephrine, histamine and acetylcholine (Stahl et al., 2003).

Traditional antidepressants including SSRIs may be relatively ineffective in this context and that *drugs targeting dopamine systems* may be more beneficial (Alexopoulos, 2001).

frontiers in Aging Neuroscience

REVIEW
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Risk Factors for Post-stroke Depression: A Meta-analysis

Yu Shi[1†], Dongdong Yang[2†], Yanyan Zeng[1] and Wen Wu[1]*

[1] Department of Rehabilitation, Zhujiang Hospital, Southern Medical University, Guangzhou, China, [2] Department of Neurology, Zhengzhou People's Hospital, Zhengzhou, China

Meta-analysis Results

Sex

A total of eight articles reported sex (female) was a risk factor for PSD in the acute stage and subacute stage (≤3 months).

Age

A total of two articles reported age (<70 years) was a risk factor for PSD in the acute stage and subacute stage (≤3 months).

Social Support

A total of three articles reported social support was a protective factor for PSD in the acute stage and subacute stage (≤3 months).

History of Mental Illness

A total of six articles reported history of mental illness (depression/anxiety/etc.) was a risk factor for PSD in the acute stage and subacute stage (≤3 months). **Figure 5** shows that there

Neuroticism

A total of three articles reported neuroticism was a risk factor for PSD in the acute stage and subacute stage (≤3 months).

Family History of Mental Illness

A total of two articles reported family history of mental illness was a risk factor for PSD in the acute stage and subacute stage

Severity of Stroke

A total of six articles reported severity of stroke was a risk factor for PSD in the acute stage and subacute stage (≤3 months).

Level of Handicap

A total of four articles reported level of handicap was a risk factor for PSD in the acute stage and subacute stage (≤3 months).

Level of Independence

A total of five articles reported level of independence was a risk factor for PSD in the acute stage and subacute stage (≤3 months).

Location

In the included studies, the left hemisphere had an association with PSD in the acute and subacute stages. Brain damage in the left frontal lobe and left basal ganglia was associated with PSD.

Early Predictors of PSD

Low Barthel Index score

http://www.strokecenter.org/trials/scales/barthel.pdf

Carota et al 2005

Age <68 years

Crying in first few days

- Pathological crying (not associated with PSD)
- Emotionalism (41% developed PSD)
- Catastrophic reaction (63% developed PSD)

Distinguishing types of crying

Pathological crying linked to infarct in basis of pontis and corticobulbar pathways and occurs in response to mood incongruent cues.

Emotionalism is crying that is congruent with mood (sadness) but patient is unable to control crying as they would have before stroke.

Catastrophic reaction is crying or withdrawal reaction triggered by a task made difficult or impossible by a neurologic deficit (e.g. moving a hemiplegic arm)

Screening Tools

Observational Measures

- **Hamilton Depression Rating Scale (HDRS)***
- Post-stroke Rating Depression Scale (PDRS)#
- Stroke Aphasia Depression Questionnaire (SADQ-H 21 or 10 item)
- Aphasia Depression Rating Scale (ADRS)
- Signs of Depression Scale (SODS; RN admin.)
- Montgomery-Asberg Depression Rating Scale (MADRS)

* Appear to have best sensitivity and internal validity
# Not validated in PSD

Self-Report Measures

- Beck Depression Inventory-2 (BDI-2)
- Hospital Anxiety and Depression Scale (HADS)
- **Center for Epidemiological Studies-Depression Scale (CES-D)***
- **Patient Health Questionnaire 9-item (PHQ-9)***
- Geriatric Depression Scale (GDS)#
- Visual-Analog Mood Scale (VAMS)#

* Appear to have best sensitivity and internal validity reliability
# Not validated in PSD

Twenty-four studies (n=2907 participants) showed that the **CES-D**, **HDRS**, and **PHQ-9** had high sensitivity for detecting PSD *Meader N et al. J Neurol Neurosurg Psychiatry 2012-304194.*

Systematic screening for PSD with the 9-item **PHQ-9** is pragmatic and has high sensitivity

Systematic screening for PSD may improve outcomes

Appendice 4.: Center for Epidemiologic Studies Depression Scale (CES-D)
(Fava, 1982)

La preghia… di dirci se nella scorsa settimana si è sentito in una delle seguenti maniere. M…

DURANTE LA S…

1. Sono stato p… preoccupa…
2. Non mi anda…
3. Ho sentito ch… l'aiuto dell…
4. Ho sentito ch…
5. Ho avuto dif…
6. Mi sono sen…
7. Ho sentito ch…
8. Avevo spera…
9. Ho pensato …
10. Ho avuto pa…
11. Il mio sonno …
12. Ero felice.
13. Ho parlato m…
14. Mi sono sen…
15. La gente non…
16. Mi sono dive…
17. Ho avuto de…
18. Mi sono sen…
19. Ho sentito ch…
20. Non ce la fa…

HAMILTON RATING SCALE FOR DEPRESSION
HAM-D - # 04…

Cognome e Nome.....

Codice Paziente.....

ISTRUZIONI GENE…
pazie…

1- UMORE DEPRESSO…
(Sentimento di tristezza, mar… sentimento di incapacità e di…

0 = Assente
1 = Manifesta questi sentime…
2 = Esprime spontaneamente…
3 = Comunica questi sentimen… cioè attraverso l'espressi… corpo, la voce e la tende…
4 = Il paziente manifesta **quasi** … menti mediante messagg…

2 - SENTIMENTI DI C…

0 = Assenti
1 = Autoaccusa, pensa di ave…
2 = Idee di colpa o ripensamen… peccaminose
3 = L'attuale malattia è una p…
4 = Ode voci di accusa o di de… allucinatorie visive a cor…

3 - SUICIDIO

0 = Assente
1 = Pensa che la vita non val…
2 = Vorrebbe essere morto … suicidarsi
3 = Idee o gesti di suicidio
4 = Tentativi di suicidio *(ogn… valutato '4')*

4 - INSONNIA INIZIAL…

0 = Nessuna difficoltà ad add…
1 = Lamenta di avere talvolta… (p. es., gli occorre più di…
2 = Ha sempre difficoltà ad a…

5 - INSONNIA CENTR…

11 - ANSIA SOMATICA
ASPETTI SOMATICI DELL'ANSIA

Gastrointestinali: secchezza delle f… indigestione, diarrea, crampi, erutta…
Cardiovascolari: palpitazioni, cefal…
Respirazione: iperventilazione, sos…
Genito-urinari: pollachiuria
Sudorazione

0 = Assente 1 = Lieve
2 = Moderata 3 = Notevole
4 = Invalidante

12 - SINTOMI SOMATICI GASTROINTESTINALI

0 = Assenti
1 = Perdita dell'appetito, ma si alim… lato o aiutato dal personale. Se…
2 = Difficoltà ad alimentarsi senza… personale. Richiede o ha bisogn… ci per i disturbi gastrointestina…

13 - SINTOMI SOMATICI G…

0 = Assenti
1 = Pesantezza agli arti, alla schien… sta, mal di schiena, dolori musc… e facile affaticabilità
2 = Se i sintomi sono molto eviden…

14 - SINTOMI GENITALI
(Sintomi quali: perdita della libido,…

0 = Assenti 1 = Lievi 2 = …

15 - IPOCONDRIA

0 = Assente
1 = Polarizzazione sul proprio corp…
2 = Preoccupazione per la propria …
3 = Frequenti lamentele, richieste …
4 = Deliri ipocondriaci (ferma co…

PATIENT HEALTH QUESTIONNAIRE - PHQ-9

Il presente questionario è importante perché ci consente di fornirLe la miglior assistenza possibile. Le Sue risposte ci aiuteranno a capire i problemi che Lei può avere. La preghiamo, perciò, di rispondere con la massima precisione possibile.

1. Durante le ultime due settimane, con quale frequenza è stato disturbato da qualcuno dei seguenti problemi?	**Mai**	**Molti giorni**	**Più della metà dei giorni**	**Quasi tutti i giorni**
a. **Scarso interesse o piacere nel fare le cose**	0	1	2	3
b. **Sentirsi giù, depresso o disperato**	0	1	2	3
c. Difficoltà ad addormentarsi o mantenere il sonno, o dormire troppo	0	1	2	3
d. Sentirsi stanco o avere poca energia	0	1	2	3
e. Scarso appetito o mangiare troppo	0	1	2	3
f. Sentirsi in colpa o di essere un fallito o di aver danneggiato se stesso o la sua famiglia	0	1	2	3
g. Difficoltà a concentrarsi sulle cose, come leggere il giornale o guardare la televisione	0	1	2	3
h. Muoversi o parlare così lentamente tanto che anche gli altri se ne accorgevano o, al contrario, essere così irrequieto o agitato da doversi muovere da ogni parte molto più del solito	0	1	2	3
i. Pensare che sarebbe meglio essere morto o di farsi del male in qualche modo	0	1	2	3

Post-Stroke Depression Rating Scale (PSDRS)

10 sezioni:

- umore depresso
- sentimento di colpa
- pensieri suicidari
- disturbi vegetativi
- apatia
- ansia
- **reazione catastrofica**
- **labilità emotiva**
- anedonia
- variazioni diurne

punteggi più elevati
= maggiore gravità

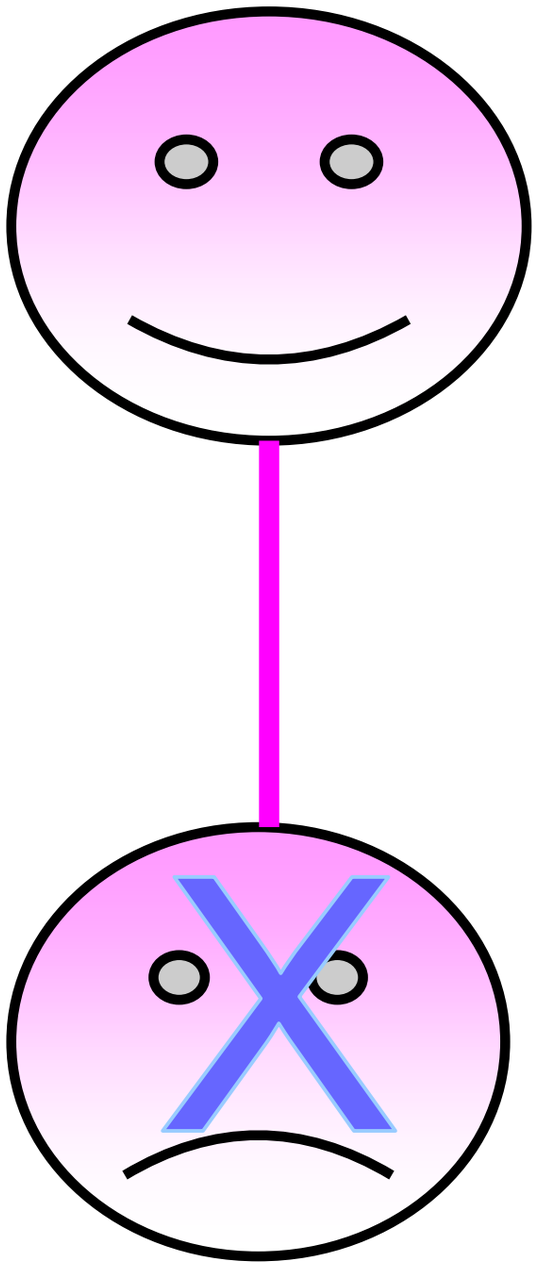
senza cut-off

strumento di profilo

Gainotti. J Clin Exp Neuropsychol 19: 340-56, 1997

Visual Analog Mood Scales: Sad scale

Stern, 1997



Sistema di valutazione non verbale

Il pz deve indicare il volto con cui si identifica

Aphasic Depression Rating Scale (ADRS)

		Ingresso	1 mese
1.	**Insonnia**		
	No	0	0
	Disturbi del sonno riferiti dal paziente o dal personale	1	1
	Deambula durante la notte, si alza dal letto o tenta di alzarsi	2	
2.	**Ansia psichica**		
	No	0	
	Tensione/irritabilità	1	
	Si inquieta per piccole cose	2	
	Apprensività evidente	3	3
	Apprensività/ansia molto evidente	4	4
3.	**Ansia somatica (*sintomi gastrointestinali, cardiovascolari, respiratori, urinari)***		
	No	0	0
	Lievi	1	1
	Moderati	2	2
	Severi	3	3
	Molto severi	4	4
4.	**Sintomi somatici gastrointestinali**		
	Nessuno	0	0
	Perdita appetito ma continua a mangiare		
	Non mangia; richiede farmaci per trattare i disturbi GI		
5.	**Ipocondriasi**		
	Assente		
	Il paziente autogestisce le sue preoccupazioni		
	Preoccupazioni manifeste		
	Frequenti richieste di aiuto		
	Ipocondriasi manifesta		
6.	**Perdita di peso**		
	Meno di 0.5 kg/settimana		
	0.5-1 kg/settimana		
	> 1 kg/settimana		
7.	**Tristezza apparente**		
	No		
	Tra 0 e 2		
	Sorride senza difficoltà		
	Tra 2 e 4		
	Triste, infelice la maggior parte del tempo	4	4
	Tra 4 e 6	5	5
	Sempre triste	6	6

8.	**Mimica facciale**		
	Muove il volto, esplora, si interessa	0	0
	Lieve riduzione della mimica facciale	1	1
	Mimica sicuramente ridotta ma comunque espressiva, volge lo sguardo intorno	2	2
	Non muove la testa, non sorride, non cambia espressione	3	3
	Immobile e inespressivo	4	4
9.	**Affaticabilità**		
	No	0	0
	Non spontanea, emerge nel corso della visita	1	1
	Presente e limitante le comuni attività (mangiare, lavarsi,vestirsi)	2	2
	Presente e tale da impedire alcune attività	3	3
	Incapacità a compiere qualsiasi attività	4	4
	TOTALE ADRS		

ADRS: Benaim *et al.*, 2004

Therapy

Interventions for treating depression after stroke

Hackett ML, Anderson CS, House AO 2008

12 RCTs of the efficacy of antidepressant medication to treat PSD (n=1121).

The data suggested a beneficial effect of antidepressants on remission (pooled OR for meeting criteria for depression : 0.45; 95% CI, 0,22-0.98) and response, measured as a >50% reduction in mood scores (pooled OR, 0.22; 95% CI 0.009-0.52)

Adverse events : CNS (OR 1.96; 95% CI, 1.19-3.24). Gastrointestinal (OR 2,37; 95% CI, 1.38-4.06). Other (OR 1,51; 95% CI, 0.91-2.3

Systematic Review and Meta-Analysis

Medicine®

OPEN

Efficacy and feasibility of antidepressant treatment in patients with post-stroke depression

Xiao-min Xu, MD[a,b], De-zhi Zou, PhD[a,b], Liu-yan Shen, MD[c], Yang Liu, MD[a,b], Xin-yu Zhou, PhD[a,b], Jun-cai Pu, MD[a,b], Mei-xue Dong, PhD[a,b], You-dong Wei, PhD[a,b,*]

2016) 95:45

Table 1

Demographic and clinical characteristics of included randomized controlled trials.

Study	Mean age (SD)	Female, %	Center	Depression criteria	Treatment groups	Intervention vs placebo (n)	Dose range, mg/d	Duration	Depression rating scale	Mean depression score (SD)	Response or remission criteria
Andersen 1994	67.0 (7.1)	61%	Multiple centers	DSM-III-R	Citalopram vs Placebo	33 vs 33	10–40	6 wk	HAMD-17	19.4 (3.1) vs 18.9 (2.8)	≥50% reduction

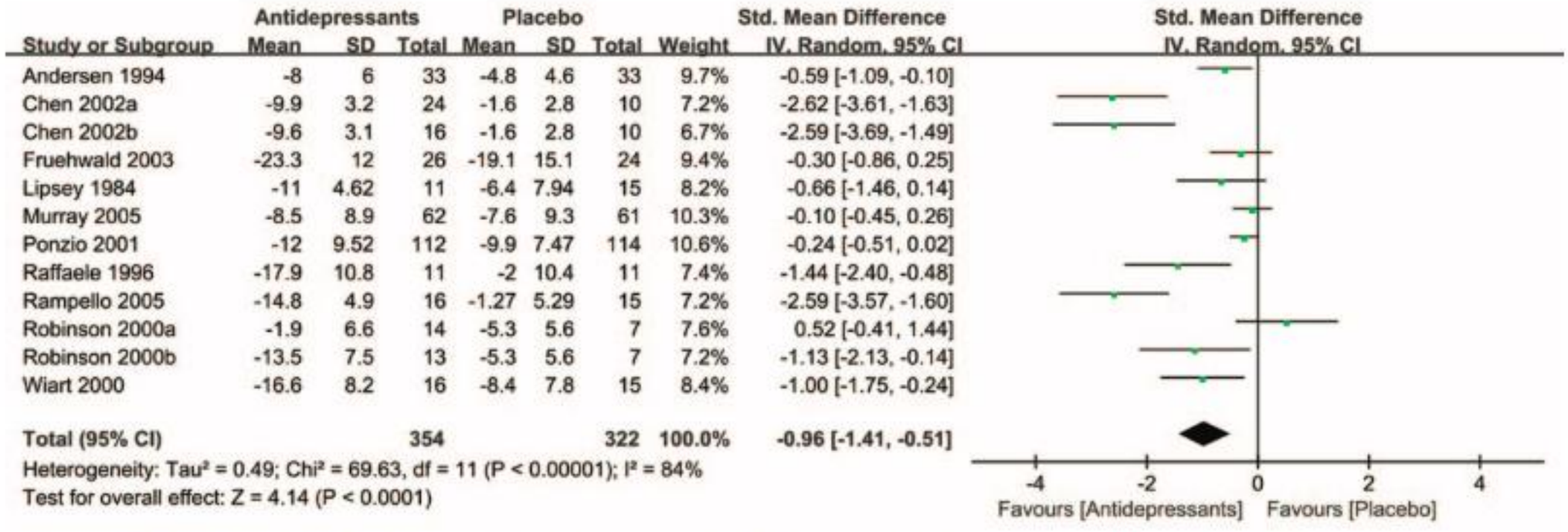
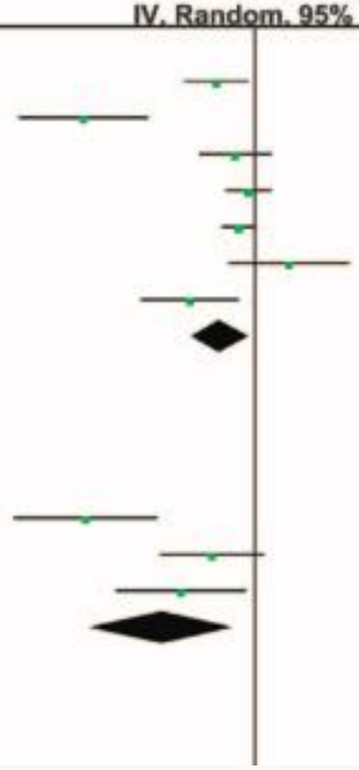


Figure 2. Effect of antidepressants in the treatment of PSD compared with placebo. PSD = post-stroke depression.

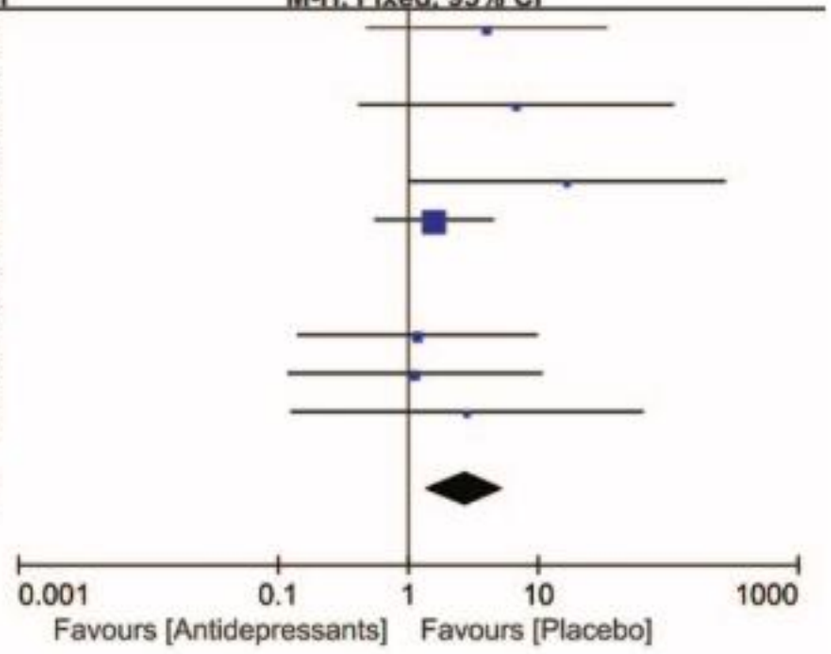
Study or Subgroup	Antidepressants Mean	SD	Total	Placebo Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
SSRI								
Andersen 1994	-8	6	33	-4.8	4.6	33	9.7%	-0.59 [-1.09, -0.10]
Chen 2002a	-9.9	3.2	24	-1.6	2.8	10	7.2%	-2.62 [-3.61, -1.63]
Fruehwald 2003	-23.3	12	26	-19.1	15.1	24	9.4%	-0.30 [-0.86, 0.25]
Murray 2005	-8.5	8.9	62	-7.6	9.3	61	10.3%	-0.10 [-0.45, 0.26]
Ponzio 2001	-12	9.52	112	-9.9	7.47	114	10.6%	-0.24 [-0.51, 0.02]
Robinson 2000a	-1.9	6.6	14	-5.3	5.6	7	7.6%	0.52 [-0.41, 1.44]
Wiart 2000	-16.6	8.2	16	-8.4	7.8	15	8.4%	-1.00 [-1.75, -0.24]
Subtotal (95% CI)			**287**			**264**	**63.3%**	**-0.53 [-0.97, -0.09]**
Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 29.88$, df = 6 ($P < 0.0001$); $I^2 = 80\%$								
Test for overall effect: $Z = 2.37$ ($P = 0.02$)								
TCAs								
Chen 2002b	-9.6	3.1	16	-1.6	2.8	10	6.7%	-2.59 [-3.69, -1.49]
Lipsey 1984	-11	4.62	11	-6.4	7.94	15	8.2%	-0.66 [-1.46, 0.14]
Robinson 2000b	-13.5	7.5	13	-5.3	5.6	7	7.2%	-1.13 [-2.13, -0.14]
Subtotal (95% CI)			**40**			**32**	**22.1%**	**-1.41 [-2.51, -0.31]**
Heterogeneity: $Tau^2 = 0.70$; $Chi^2 = 7.84$, df = 2 ($P = 0.02$); $I^2 = 74\%$								
Test for overall effect: $Z = 2.52$ ($P = 0.01$)								

Std. Mean Difference
IV, Random, 95% CI



Study or Subgroup	Antidepressants Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andersen 1994	4	33	1	33	9.6%	4.00 [0.47, 33.91]
Chen 2002a	0	24	0	12		Not estimable
Chen 2002b	6	24	0	12	6.3%	6.76 [0.41, 110.86]
Fruehwald 2003	0	28	0	26		Not estimable
Lipsey 1984	6	17	0	22	4.2%	16.61 [1.00, 275.78]
Murray 2005	8	62	5	61	48.6%	1.57 [0.55, 4.54]
Rampello 2005	0	16	0	15		Not estimable
Reding 1986	0	11	0	6		Not estimable
Robinson 2000a	3	23	1	9	13.9%	1.17 [0.14, 9.86]
Robinson 2000b	2	16	1	9	12.3%	1.13 [0.12, 10.75]
Wiart 2000	1	16	0	15	5.0%	2.82 [0.12, 64.39]
Total (95% CI)		**270**		**220**	**100.0%**	**2.72 [1.37, 5.43]**
Total events	30		8			
Heterogeneity: $Chi^2 = 4.34$, df = 6 ($P = 0.63$); $I^2 = 0\%$						
Test for overall effect: $Z = 2.85$ ($P = 0.004$)						

Risk Ratio
M-H, Fixed, 95% CI



B

Figure 4. Acceptability of antidepressants in the treatment of PSD. A, Withdrawals for any reason between antidepressants and control groups. B, Withdrawals for adverse events between antidepressants and control groups.

Tricyclic ADs (**TCAs**)

Amitriptyline has similar in vitro reuptake inhibitory potencies for 5-HT and NA

Nortriptyline is preferentially a NA reuptake inhibitor. Both are also 5-HT2 receptor antagonists.

Meta-analysis with a total of 40 cases treated with TCAs vs. 32 with placebo, found a significant advantage of TCAs over placebo (SMD = 1.41; 95% CI = 2.51 to 0.31; P=0.01).

Xu et al.2016,

Caution in elderly stroke patients due to possible occurrence of

Orthostatic hypotension

Cardiac arrhythmia

Or in presence of glaucoma and prostate hyperplasia

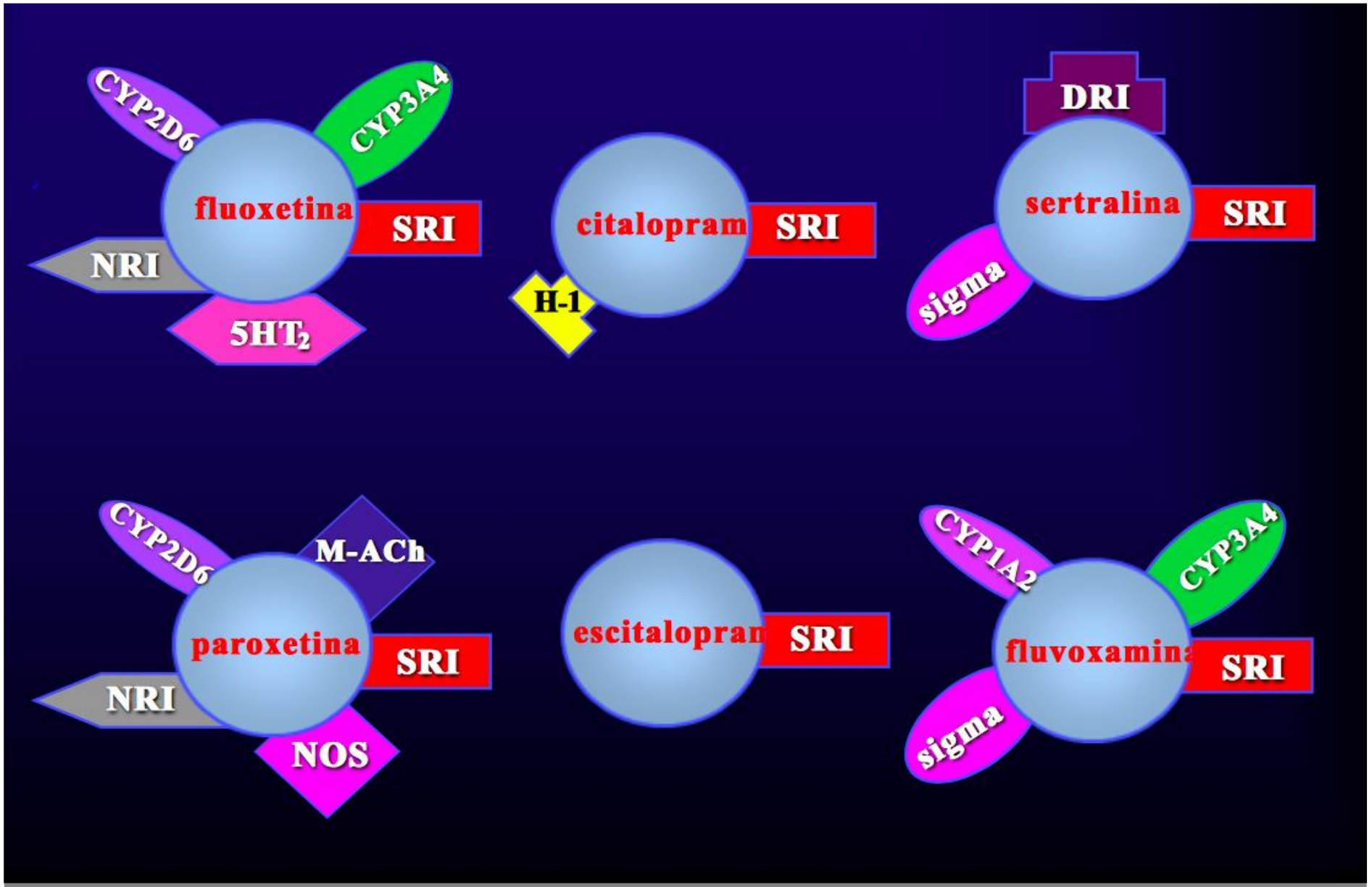
Anticholinergic activity, (scoring 3 at Anticholinergic Burden Scale, the maximum score for risk of occurrence of delirium)

TCAs are not recommended as first-line choice for treatment of PSD.

Selective serotonin reuptake inhibitors (**SSRIs**)

The meta-analysis reported 7 trials, with a total of 287 patients treated with SSRIs vs 264 with placebo

Significant advantage of SSRIs versus placebo (SMD= 0.53; 95% CI=0.97 to 0.09; P=0.02)



Optimal length of treatment: the suggested length of 4-6 months is essentially an opinion of experts

Xu et al. 2016

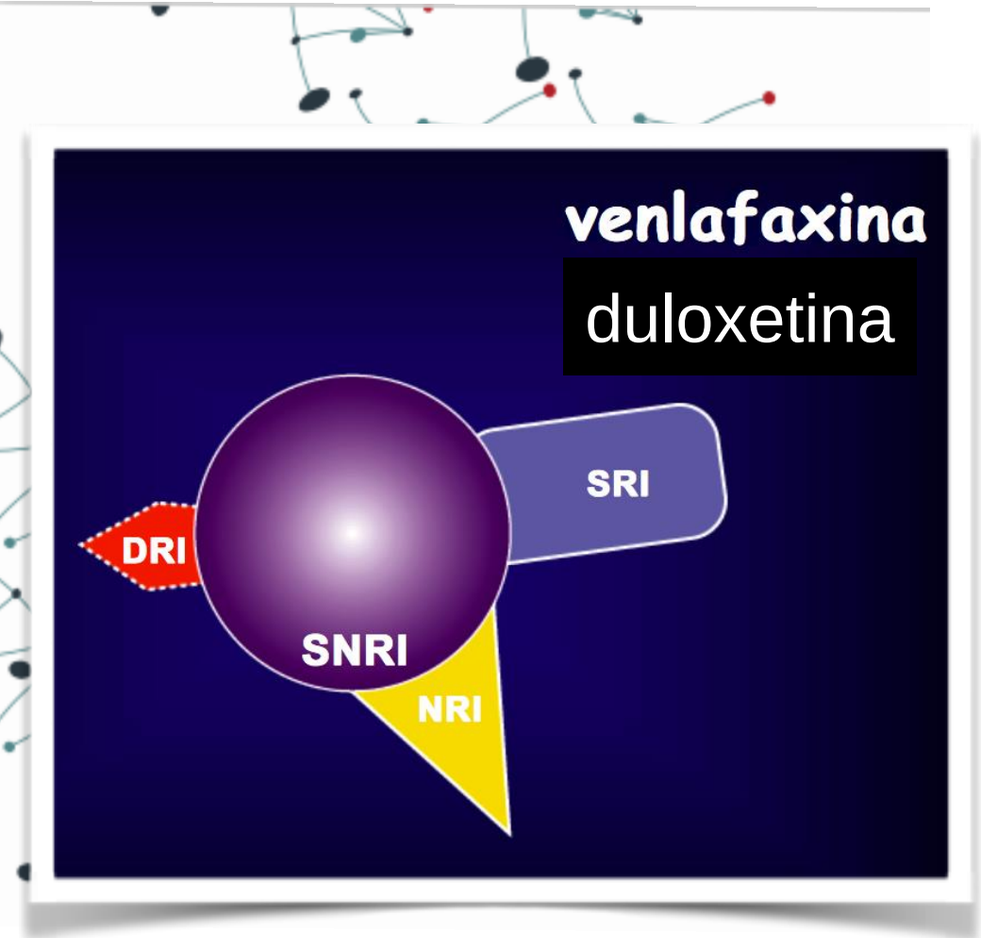
Risk of intracerebral hemorrhage

Almost all serotonin in blood is contained in dense granules inside platelets. Selective serotonin reuptake inhibitors decrease these platelet serotonin stores, which can limit platelet adhesion in the setting of endothelial disruption

…a meta-analysis confirmed this risk, it also defined it to be very low (“....1 additional intracerebral bleeding episode per 10,000 persons treated for 1 year....”)

Hackam DG, Mrkobrada M. Neurology 2012;79:1862-1865.

- ICH modestly increased compared with TCAs (1.17; 95% CI, 1.02- 1.35)
- Risk highest during the first month of use.
- Strong inhibitors such as fluoxetine, paroxetine, and sertraline had an RR of 1.25 (90% CI, 1.01-1.54) compared with weak inhibitors
- ***Anticoagulant medications*** increased the risk of SSRIs compared with TCAs, although this result was not statistically significant
- Antiplatelet agents did not modulate this effect of SSRIs on intracranial bleeding.

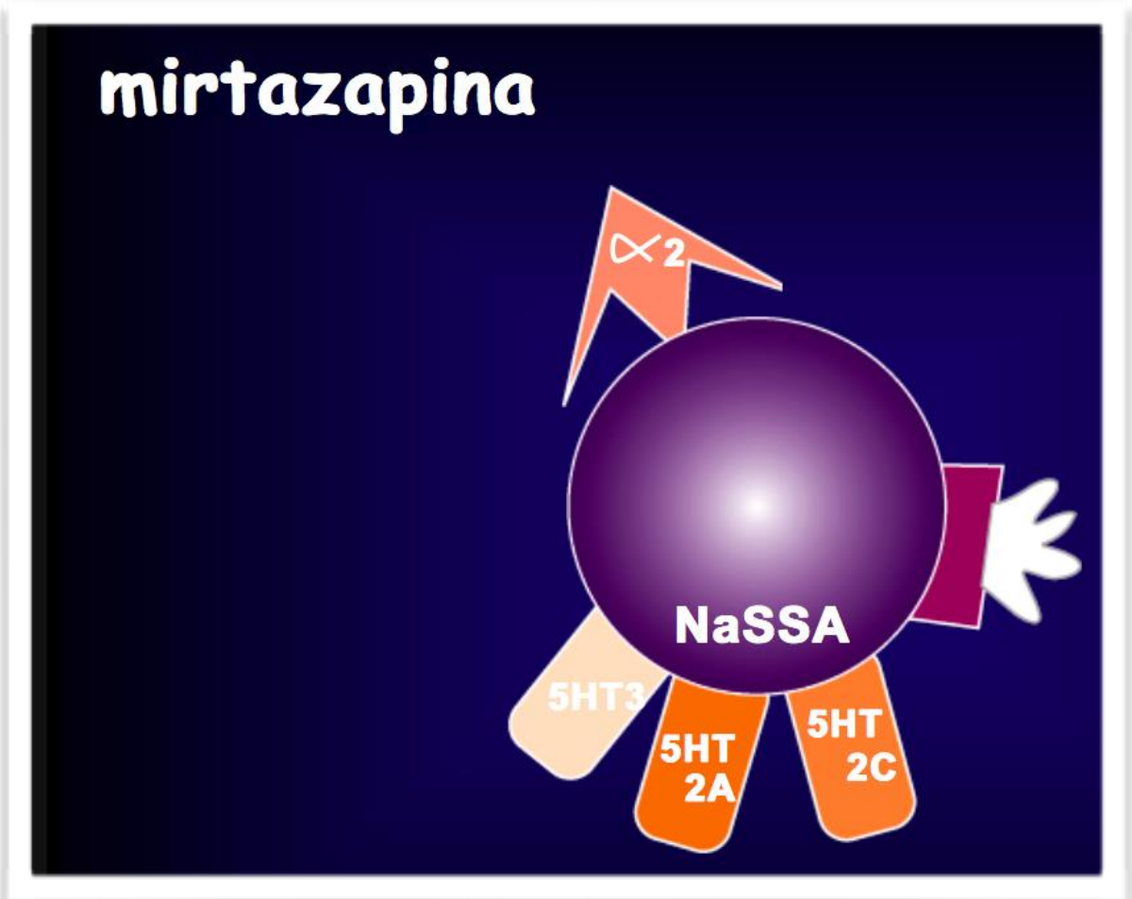


- Improving painful physical symptoms due to their noradrenergic action
- Patients treated with duloxetine compared with those treated with sertraline and citalopram, showed a greater and faster improvement in depressive symptoms and a better response on anxiety symptoms. *Karaiskos D.J Neuropsychiatry Clin Neurosci 2012;24:349-353.*
- Prophylactic use of duloxetine decreased the incidence of PSD, promoted rehabilitation, cognitive function and quality of life *Zhang LS Eur Neurol 2013;69:336-343.*
- Similar risk of intracranial hemorrhage

Efficacious in preventing and treating PSD *Niedermaier N.. J Clin Psychiatry 2004;65:1619- 1623.*

Sedation

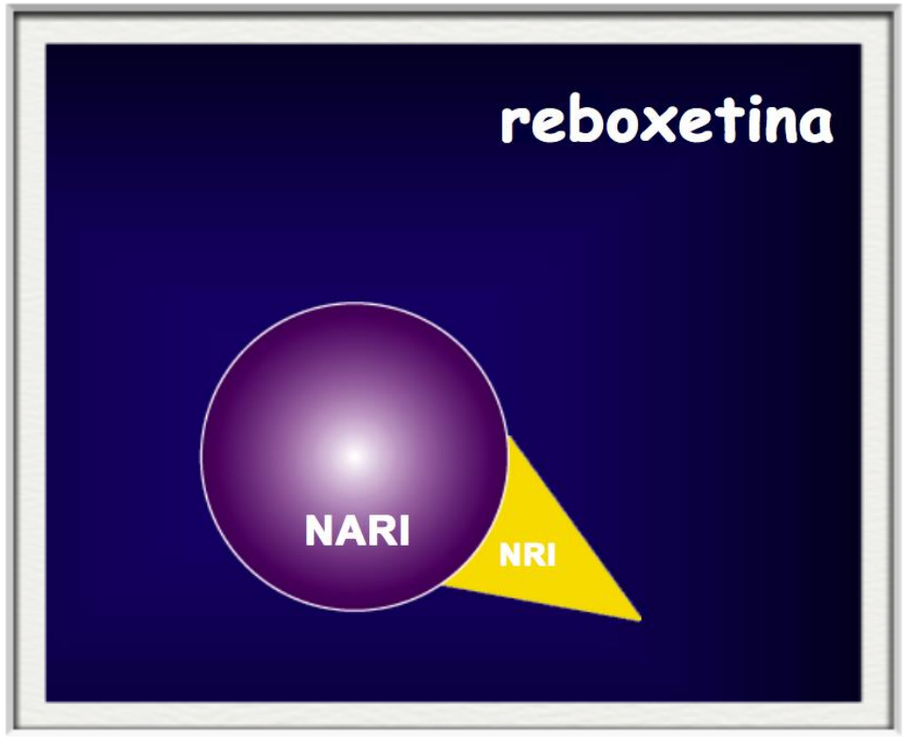
Weight gain

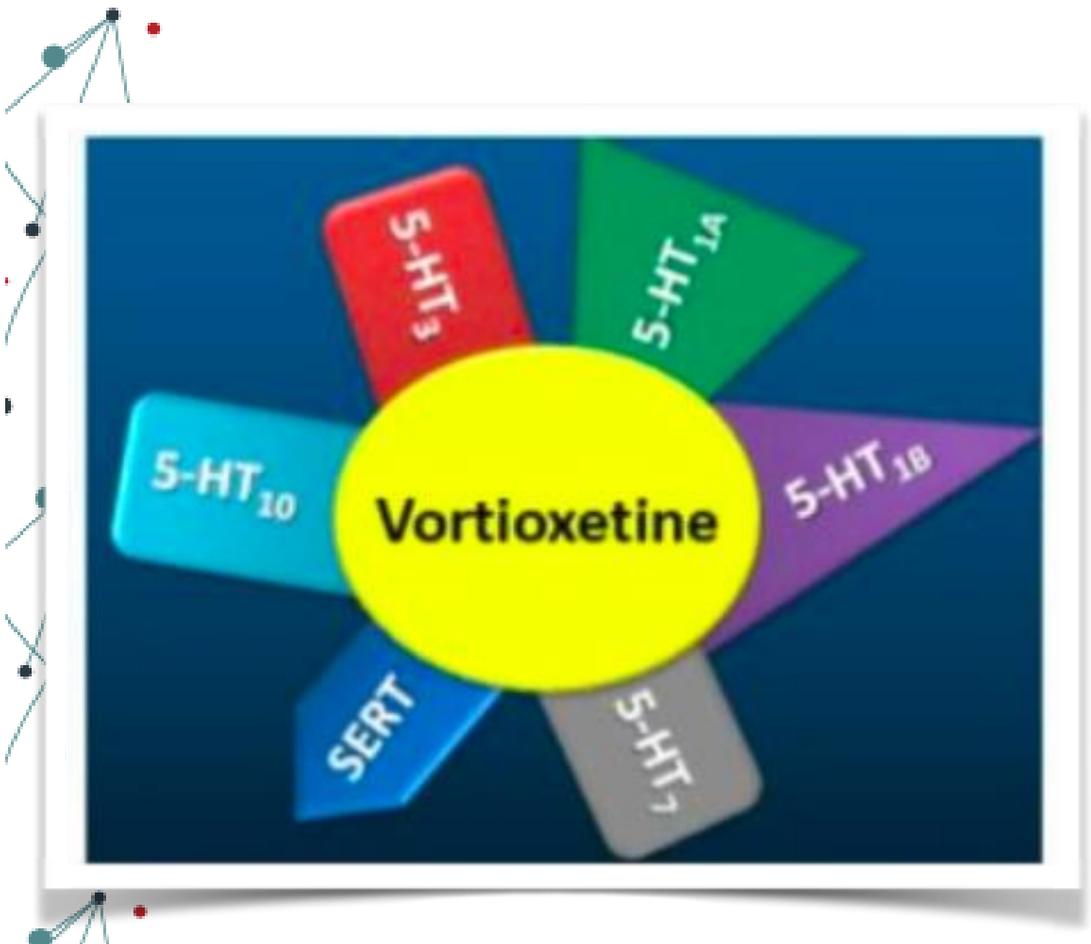


- Greater efficacy in PSD patients affected by "delayed" depression, as compared with citalopram

- More efficacious in patients with anxious depression

Rampello L. Psychopharmacology (Berl) 2004;173:73- 78.





- A recent meta-analysis on three DB-RCT, found that vortioxetine significantly improved cognition, independently by depressive symptoms

- Improvements in measures of executive function, attention/speed of processing, and memory. *McIntyre RS Int J Neuropsychopharmacol 2016*

- Coadministration of vortioxetine, even if in healthy volunteers, had no effect neither on aspirin or warfarin pharmacokinetics or pharmacodynamics nor on arterial blood pressure and cardiac parameters including QTc *Harrison JE,. Int J Neuropsychopharmacol 2016*

Prevention of PSD Using Pharmacological Interventions

2008 Cochrane systematic review including 12 placebo-controlled trials of 611 individuals, finding no evidence that antidepressant drugs prevented depression after stroke. Cochrane Database Syst Rev. 2008.

A meta-analysis: 8 RCTs (from 1990 through 2011)
preventive pharmacological interventions among 776 initially non depressed stroke patients.
PSD was reduced among patients receiving active pharmacological treatment
no significant differences between the active treatment and placebo groups in the *frequency of side effects. Salter et al. J Stroke Cerebrovasc Dis 2013*

ISO
ITALIAN STROKE ORGANIZATION

Raccomandazione 15.9 **Forte contro** **Grado A**

Allo stato attuale non è raccomandato alcun trattamento farmacologico o psicoterapico per prevenire l'insorgenza della depressione post-ictus.

Recommendations: Poststroke Depression, Including Emotional and Behavioral State	Class	Level of Evidence
The usefulness of routine use of prophylactic antidepressant medications is unclear.	IIb	A

Stroke **June 2016 Winstein et al Guidelines for Adult Stroke Rehabilitation and Recovery**

Highlights

PSD is a negative, but modifiable risk factors “quoad vitam” and “quoad valetudinem”

Screening to everyone, acute and serially

Antidepressants are efficacious for stroke survivors with PSD

SSRI: Citalopram, escitalopram and sertraline are to be preferred because of a lower risk of ***drug interactions***

Choose an AD on the basis of ***clinical features of depressive symptoms***

- Noradrenergic/dopaminergic action: symptomatology of hypoactivation/DED
- Serotonergic drug: anxious symptoms.
- SNRIs: pain related symptoms
- Mirtazapine: sedative-hypnotic properties, increase the appetite and weight.
- Vortioxetine improved cognition, no effect on aspirin or warfarin