老年人憂鬱症的治療與處方原則

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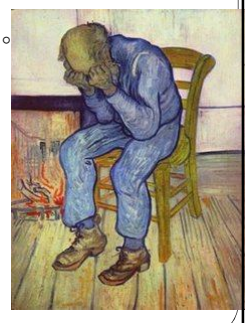
我有重度憂鬱症嗎？

- 憂鬱情緒，對諸多事情缺乏興趣
  達2週以上。

1.失眠（或嗜眠）
2.無食慾、體重減輕（或食慾大增，體重增加）
3.無精力、動作思考緩慢。
4.激躁不安、注意力不集中、無法決定事情。
5.罪惡感。
6.無助無望感、自殺意念或行為。



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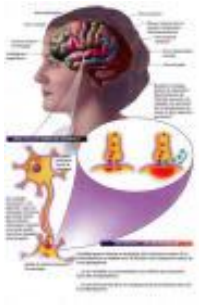
憂鬱症的成因？-1

- 生物因素：
  - 腦功能-
    - 邊緣系統（limbic system)
    - 神經傳導介質（neurotransmitter):
      血清素（serotonin）
      正腎上腺皮質素（norepinephrin)
      多巴胺(dopamine)
  - 賀爾蒙與內分泌系統-



3

邊緣系統

- *統管情緒、身體、性慾與壓力反應。*
  - *下視丘：統管體溫、睡眠、食慾、性慾、壓力反應、腦下垂體（調節賀爾蒙）*
  - *杏仁核（amygdala）*
  - *海馬回（hippocampus）*

4

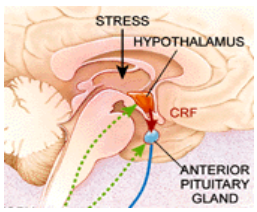
神經傳導介質

- 血清素↓
- 正腎上腺皮質素↓
- 多巴胺： ↓ mesocortical,mesolimbic dopamine →cognitive, motor, and hedonic disturbances associated with depression .

5

內分泌系統

- 下視丘（經由神經傳導物質） → 腦下垂體 → 分泌各種賀爾蒙
- 下視丘（CRH) →腦下垂體（ACTH)→ 腎上腺分泌可體松（cortisol)濃度居高不下



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憂鬱症的成因？-2

- 基因：
  - 雙親中有一位是情感性精神病患者，其子女得重鬱症的機率是25%。
  - 若兩個均是患者，子女得病的機率升至50-75%。
  - 若雙親或手足有一位得重鬱症，則有1.5-3倍得重鬱症的機會。

7

憂鬱症的成因？-3

- 社會心理因素：
  - 工作壓力、親人失落、創傷事件等
  - *kindling-sensitization hypothesis*.–初次的憂鬱發作，改變邊緣系統與腦內生化，讓接續的憂鬱症更容易發生。
  - *learned helplessness*
  - 童年不愉快：性、身體虐待，跟父母分開、父母親生病等。11歲以前的分離或死別。

8

壓力與疾病

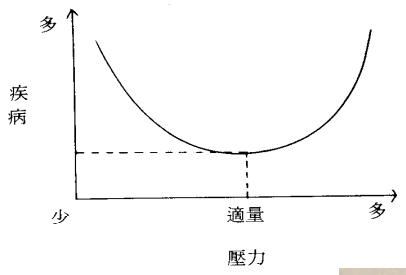


圖1－2　壓力與疾病的關係圖

9

Etiology of Geriatric Depression:

Intrinsic Factors (1/2):

1. Genetic factors
2. Age-related neurochemical changes
3. Age-related neuroanatomical changes
4. Reduction of cerebral flow
5. Vascular factor

Etiology of Geriatric Depression:

Intrinsic Factors (2/2):

6. Physical illness
7. Medications
8. Pain
9. Sleep disturbance

Etiology of Geriatric Depression:

External Factors:

1. Psychosocial stress and coping
2. Bereavement
3. Family and social support

Etiology of Geriatric Depression:

Problems in Late life

1. Sensory deprivation
2. Self-image
3. Self-esteem
4. Space/ territory
5. Separation/ loss

Treatment of Geriatric Depression

憂鬱症診治的重要觀念與原則

1. 重鬱症是腦部疾病，應以治療一般疾病的診治態度，積極面對
2. 儘早獲取正確的診斷
3. 提供各種治療模式及全面性的服務
4. 社會心理處遇對輕度重鬱症有療效
5. 醫療治療不排除社會心理處遇，憂鬱症治療亦然
6. 生物治療(biological treatment 如藥物)是憂鬱症治療的主力

Psychosocial Treatment for Geriatric Depression

Evidence-Based Pharmacologic Interventions for Geriatric Depression

Shanmugham B, et al., Psychiatric Clinic of North America 2005

Table 1
Treatment strategies in geriatric major depression

Intensity	Treatment strategy (A, D)
Major depression	Antidepressant alone
	Antidepressant and psychotherapy
Mild depression	Antidepressant and psychotherapy
	Antidepressant alone or psychotherapy alone

A, directly based on category I evidence; D, directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence.

Treatment for Geriatric Depression:

Psychosocial Intervention

1. Reality orientation
2. Attitude therapy
3. Remotivation
4. Resocialization
5. Sensory retraining
6. Reinforcement therapy
7. Self-image therapy

Treatment for Geriatric Depression:

Life Satisfaction in Late Life

- Economic dependence
- Parenthood
- Goal achievement
- Personality type
- Health
- Social activities
- Religion

Treatment forGeriatric Depression:

Psychosocial Intervention

- The climate of acceptance
- A bridge to reality
- Sharing the world we live in
- Appreciation of the work of the world

Developing an intervention for depressed, chronically medically ill elders

Alexopoulo GS, et al., Int J Geriat Psych, 2008

- An intervention that identifies and directly addresses barriers to treatment adherence and also imparts skills necessary for problem-solving can offer the behavioral platform through which specific treatments can be administered.

Biological Treatment for Geriatric Depression

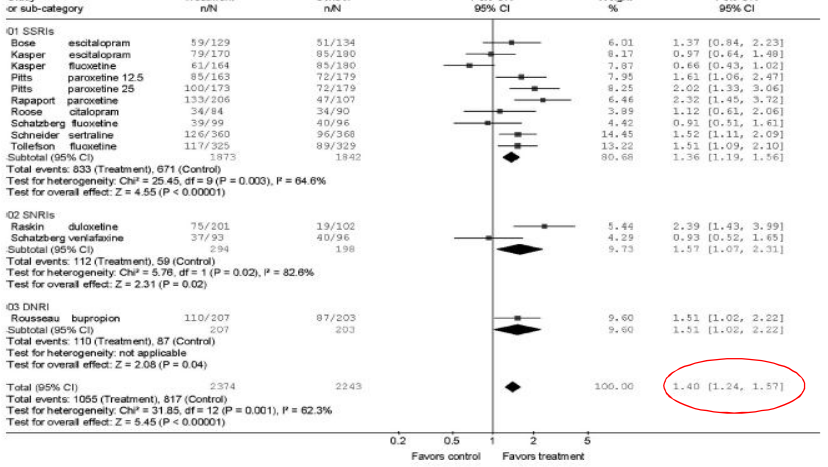
Treatment of Geriatric Depression:

Biological treatment for depressed elderly

1. Antidepressants:
2. Electro-convulsive therapy

Antidepressants response in old age depression

FIGURE 2. IIT/LOCF Response Rates by Individual Trial, Drug Class, and Overall Compared with Placebo



24

Nelson JC et al: Am J Ger Psychiatry 2008; 16:558-67.

Meta-analysis

- 10 unique trials (4 unpublished), 6-12 wks
- Active drugs n=2377, PBO n=1788
- Odds ratio for response 1.40 (1.24-1.57, $p \leqq 0.001$)
- Odds ratio for remission 1.27 (1.12-1.44, $p \leqq 0.001$)
- Mean pooled response:

active drug 44.4% vs. PBO 34.7%

Nelson JC et al: Am J Ger Psychiatry 2008; 16:558-.

25

抗憂鬱藥使用原則

- 抗憂鬱藥非專科用藥，各科醫師皆可開立
- 除單胺氧化酶(monoamine reuptake inhibitor)外，所有抗憂鬱藥都可以是首選藥物
- 個案過往有效的藥物為優先考量
- 考量藥理作用
- 考量副作用
- 個案的喜好也是考量之一。

選藥考慮因素

- 個案年紀
- 伴隨身體疾病
- 併服之其他藥物
- 症狀
- 以往對抗憂鬱藥的反應
- 藥物副作用
- 個案對副作用的耐受性
- 個案的喜好
- 費用

Treatment of Geriatric Depression:

- All antidepressants show the equal efficacy in the treatment of depression
- Drug of choice would be better to dependent on pharmacokinetic characteristics and side effect profiles

Guideline P.19

依身體狀況考慮的選藥原則

(a) 肝臟疾患：

建議降低起始劑量，減緩加量速度，並隨時評估其副作用

(b) 腎臟疾患：

建議增加劑量速度減緩，並隨時評估其副作用。

中重度腎功能障礙者最高劑量建議減少25% ~50%

(c) 癲癇：

使用 TCAs, maprotiline及NDRI 宜小心

(d) 心臟疾病：

SNRIs, SSRIs, NDRI, agomelatine可安全使用於心臟疾病

Table 8–3. Comparison of average immunoquantified levels of the various P450s in liver microsomes with the estimated participation in drug metabolism

Cytochrome P450	Average immunoquantified level of P450 in human liver microsomal samples (%)[a]	Estimated participation in drug metabolism (%)[b]
1A2	13	<10
2A6	4	<10
2B6	0.2	(Marginal)
2E1	7	<10
2C	18	10
2D6	1.5	30
3A	29	50
Unidentified	27.3	
	Total 100	

[a]Shimada et al. 1994.
[b]Benet et al. 1996; Wrighton and Stevens 1992.

TABLE 2. Substrates, Inducers, and Inhibitors of Major Human Cytochromes

Cytochrome	Substrates	Inducers	Inhibitors
CYP3A4	Alprazolam, astemizole, atorvastatin, carbamazepine, cisapride, cyclosporine, diltiazem, losartan, lovastatin, midazolam, nifedipine, simvastatin, terfenadine, theophylline, verapamil	Carbamazepine, ethanol, phenobarbital, phenytoin, rifampin, St. John's wort	Cimetidine, clarithromycin, cyclosporine, diltiazem, erythromycin, fluoxetine, fluvoxamine, grapefruit juice, human immunodeficiency virus protease inhibitors, itraconazole, ketoconazole, nifedipine, verapamil
CYP2D6	Codeine, dextromethorphan, flecainide, fluoxetine, haloperidol, metoprolol, paroxetine, perphenazine, propranolol, sertraline, timolol, tricyclic antidepressants, venlafaxine		Cimetidine, dextromethorphan, fluoxetine, haloperidol, paroxetine, sertraline
CYP2C9	Diclofenac, glipizide, ibuprofen, losartan, phenytoin, tolbutamide, torsemide, warfarin	Phenobarbital, rifampin	Amiodarone, cimetidine, fluconazole, fluoxetine, itraconazole, ketoconazole, metronidazole, ritonavir
CYP2C19	Diazepam, imipramine, nelfinavir, omeprazole, pantoprazole, propranolol		Fluoxetine, fluvoxamine, omeprazole, ritonavir, sertraline
CYP2E1	Acetaminophen, ethanol	Disulfiram	Ethanol, isoniazid
CYP1A2	Caffeine, theophylline, tricyclic antidepressants, warfarin	Charbroiled food, omeprazole, phenobarbital, phenytoin, tobacco smoke	Fluvoxamine, grapefruit juice, quinolone antibiotics

常用抗憂鬱藥之潛在藥物交互作用
Interact with cytochrome P 450

Guideline P.33
表5

很少或輕度

- Citalopram
- Escitalopram
- Mirtazapine
- Venlafaxine

中度

- Bupropion (2D6)
- Duloxetine (2D6)

高度

- Fluoxetine (2D6, 2C19)
- Fluvoxamine (1A2, 2C19, 3A4)
- Paroxetine (2D6)
- Sertraline (2D6)

註： 藥物對 cytochrome P450 的影響極複雜，包括刺激、抑制及本身之被代謝 (APA, 2010)。本指引僅參考擷取 CANMAT 中最簡要之提示圖 (Lam, et al.,2009)。

- There is insufficient evidence to recommend the use of benzodiazepine augmentation of antidepressants.

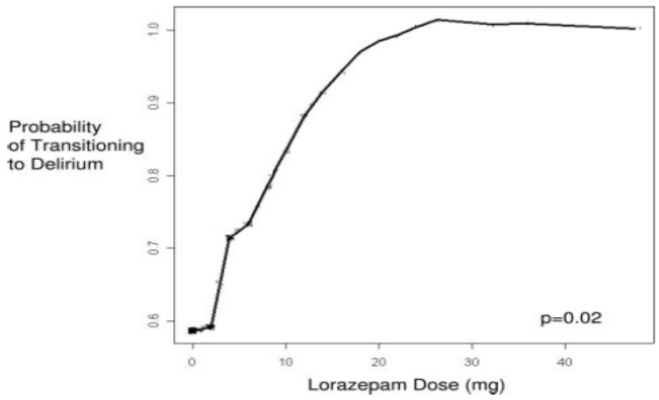
NICE, guideline for Depression, 2004

- BZDs should not usually be used beyond 2-4 weeks

NICE guideline for Generalized Anxiety Disorder, 2004

- Benzodiazepines are associated with a less good outcome in the long term and should not be prescribed for the treatment of individuals with panic disorder.

NICE guideline for Panic Disorder, 2004



Lorazepam is an independent risk factor for transitioning to delirium in the ICU. The probability of transitioning to delirium increased with the dose of lorazepam administered in the previous 24 h. This incremental risk was large at low doses and plateaued at approximately 20 mg/d

-- Pandharipande et al.2006

Benzodiazepines 併用原則

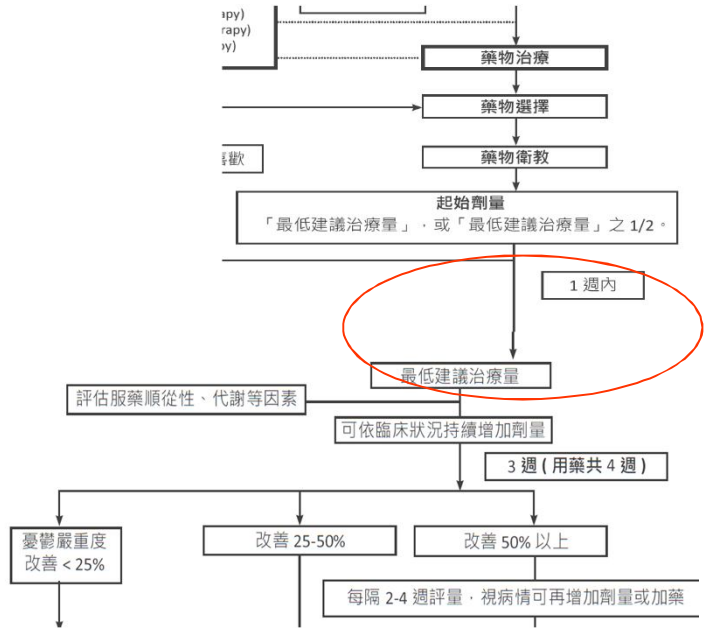
- 抗憂鬱藥有抗焦慮作用，原則上不需併用BZDs。
- 然抗憂鬱藥治療初期療效尚未出現，且部分個案焦慮症狀可能略為加重，故可併用BZDs。
- 考慮BZDs之耐受性及成癮性，建議採低劑量短期服用，勿超過 4週。

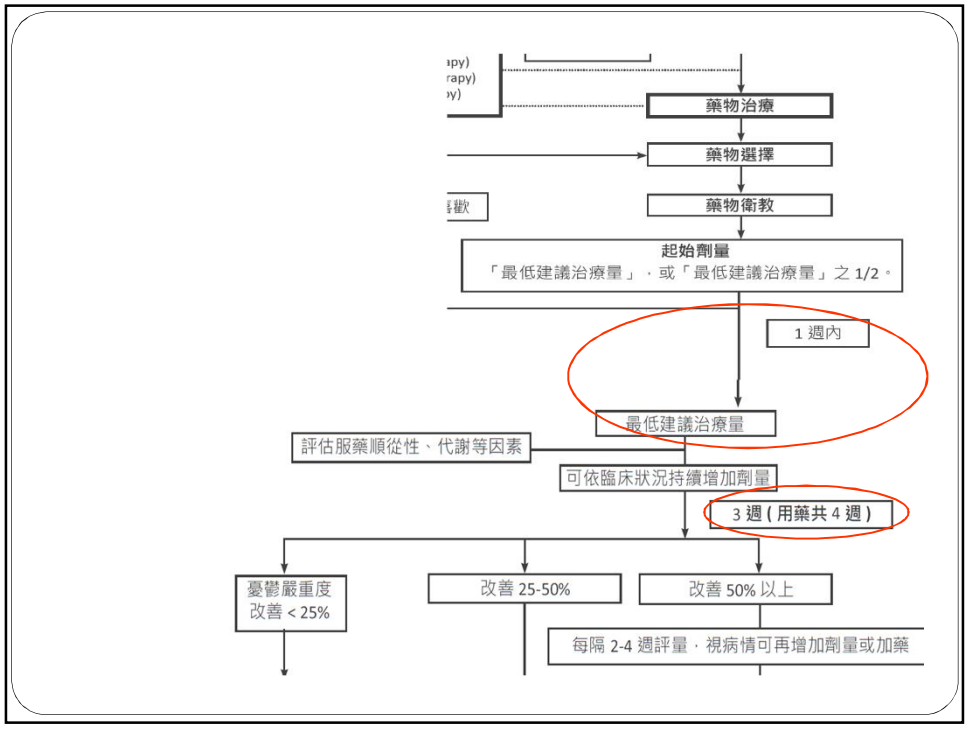
抗憂鬱劑之使用原則

- 依抗憂鬱藥之特性及個案之耐受性，可以”最低建議治療量”，或低於”最低建議治療量” 之劑量為起始劑量。
- 宜於一週內達到”最低建議治療量”之劑量。
- 抗憂鬱藥之療效需2周才能顯現出來，若療效不明顯，應(1)重新評估並確定診斷無誤，(2)確認個案服藥依從性(adherence)，(3)注意藥物動態學因素(吸收、代謝及與其它食物藥物之交互作用。

換藥或加藥

- 抗憂鬱劑使用 1+3週 無明顯進步則考慮改變治療策略。
- No response (幾乎沒進步，或進步有限) ➔ switching
  換藥以不同藥理作用的抗憂鬱藥為優先
- Partial response ➔ increased dosage





憂鬱症診治策略

Add-on strategy for partial responder

Combination：

Antidepressant + antidepressants

Augmentation

Antidepressant + other medications

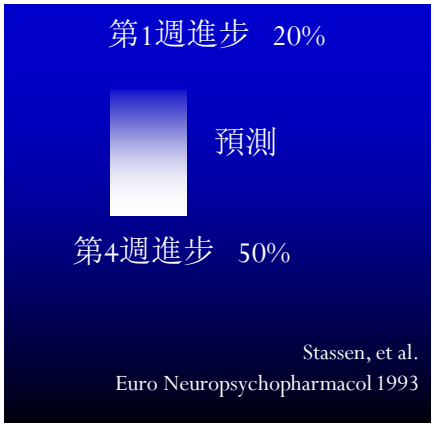
If at First You Don't Succeed

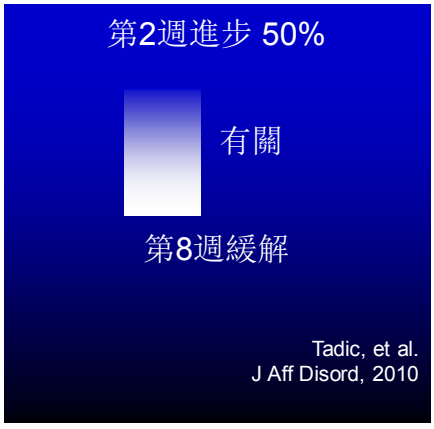
A Review of the Evidence for Antidepressant Augmentation, Combination and Switching Strategies

K. Ryan Connolly[1] and *Michael E. Thase*[1,2]

- Quetiapine and aripiprazole augmentation, or a switch to another first-line antidepressant, have the most unequivocal support, and we recommend these as first-line options. (olanzapine)
- Lithium and T3, preferred agents to augment TCA nonresponse, may well improve the efficacy of more modern medications; however, high-quality studies of these strategies are needed before they can be given unreserved recommendations.
- The use of traditional psychostimulants for augmentation is understudied.
- Antidepressant combinations are understudied
- Neither pindolol nor buspirone can be recommendedfor augmentation.

早期療效與臨床治癒有關
Early improvement predicts response





Review

Structural brain abnormalities in major depressive disorder: A selective review of recent MRI studies

Valentina Lorenzetti [a,b,c,e], Nicholas B. Allen [b,c,d], Alex Fornito [a], Murat Yücel [a,b,c,*]

- Volumetric reductions of the hippocampus, basal ganglia and prefrontal cortex are consistently found in MDD patients
- with more persistent forms of MDD (e.g., multiple episodes or repeated relapses, longer illness duration) being associated with greater impact on regional brain volumes.
- 多次發病或病程較長的抑鬱症患者，腦容積減少更多

Reflections

- In the treatment of medical diseases, e.g., hypertension, diabetes mellitus, epilepsy, …, combination therapy (polypharmacy) is a common strategy.
- "Speed" (rapid response) should be an important consideration in the treatment of major depressive disorder
- Not only for restoring functional, but also for preventing brain cell loss

Liu CY, 2011 AsCNP

抗憂鬱劑之使用原則

- 第4 週- 必須個案主觀上有進步，若主觀進步不多，或客觀量表評估進步<25%，應換藥。

  進步25-50%，可增加劑量，或再加另一藥物。

- 第10 週- 必須個案及客觀量表評估都有50% 以上之進步，否則即應增加藥量，或再加另一藥物。

台灣憂鬱症防協會 depression Rx guideline

Duration of treatment

- 治療期間：建議症狀完全緩解後再服用4~6 (9) 個月，再逐步減藥。(APA, 2010; NICE, 2004)
- 長期治療：發作兩次以上或第一次發病但病症較重(尤其功能損傷嚴重)者，宜予以維持治療(Maintenance treatment)至少 2-5 年 (APA, 2010; NICE, 2004; CINP, 2006)

Life-saving treatment for depression in elderly

Sherman FT. Geriatrics. 2009

- Always think of electroconvulsive therapy
- Electroconvulsive therapy (ECT) can be both a life-enhancing and life-saving procedure in the elderly.
- Don't forget to think about recommending ECT in an elderly depressed patient who is suicidal or has failed multiple courses of antidepressants and is doing poorly

憂鬱症之治療目標

- 治療應該達成下列各方面的改善：

(1)治療的品質，

(2)治療的滿意度，

(3)健康的治療成果，

(4)恢復功能，

(5)恢復經濟生產力，

(6)合理花費。

WHO, 2005; APA, 2010

SSRI/ SNRI discontinuation syndrome

- typically appear within three days of stopping antidepressant medication
- it has been reported that reactions may occur within hours of the missed dose
- symptoms are usually mild and resolve spontaneously in one to two weeks

Warner C, 2006

Flu-like symptoms
- Fatigue
- General malaise
- Muscle aches/headaches
- Diarrhea

Insomnia

Nausea

Imbalance
- Gait instability
- Dizziness/light headedness
- Vertigo

Sensory disturbances
- Paresthesia
- "Electric shock" sensations
- Visual disturbance

Hyperarousal
- Anxiety
- Agitation

Management for SSRI/ SNRI discontinuation syndrome

- 和緩減藥 taper gradually

  - dosage, interval

- Short term or

  p.r.n. use of benzodiazepine

Thank you very much