GIMBE®
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Workshop
Decisioni Cliniche e Prove di Efficacia
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Medicina Persona

Workshop Clinici Interattivi (2)

La depressione in Medicina Generale

Conosciamo solo la punta dell'iceberg?

Silvio Guidi

Discussant
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Scenario Clinico (1)

• La signora Daniela, 37 anni, è impiegata part-time presso uno studio tecnico.

• Due gravidanze a termine con parto eutocico, la seconda delle quali complicata da metrorragia post-partum, trattata con revisione chirurgica.

• Ha una vita moderatamente attiva e coltiva anche alcuni interessi, in particolare il canto.

Scenario Clinico (1)

• Ai primi di ottobre 2002, la signora Daniela viene in ambulatorio per la comparsa, da alcuni giorni, di un dolore intenso alla "bocca dello stomaco", che si irradia lateralmente.

• Il dolore persiste a lungo (diverse ore) durante la giornata e non trae particolare beneficio dall'assunzione di cibo; si attenua lievemente con l'eruttazione e qualche volta dopo la defecazione.

• Quando il dolore è insorto improvvisamente durante la notte, con disposizione a barra subito sotto lo sterno, la signora Daniela non è più riuscita a prendere sonno.

Scenario Clinico (1)

• Obiettivamente, avverto alla palpazione una diffusa reazione di resistenza con dolorabilità in regione epigastrica.

• Prescrivo terapia sintomatica per dieci giorni:
  - domperidone 10 mg una cpr tre volte/die, 30 minuti prima dei pasti
  - magaldrato 10 ml tre volte/die, dopo i pasti

• Dopo un paio di settimane, la signora Daniela, riferisce scarsi benefici dalla terapia ed una più precisa localizzazione della sintomatologia "alla bocca dello stomaco".

Scenario Clinico (1)

• Prescrivo una EGDS con ricerca bioptica di Hp, senza sospendere il trattamento.

• EGDS: "Nulla all'esofago ed al fondo gastrico, lieve iperemia mucosa in sede antrale, negativa la ricerca di Hp. Conclusioni: diagnosi di gastrite antrale, si consiglia terapia con inibitori di pompa per un mese.

• Prescrivo omeprazolo 20 mg/die e rassicuro la signora Daniela: "vedrà che questa è la cura giusta".

Scenario Clinico (1)

• Dopo circa quattro settimane, vengo svegliato intorno alle tre di notte dal telefono che squilla insistentemente: il marito della signora Daniela, con voce concitata, mi prega di andare a casa sua perché la moglie, da circa un ora, lamenta un severo dolore toracico con difficoltà a respirare e sensazione di svenimento.

• Al mio arrivo, la signora Daniela, distesa sul letto, ha un aspetto molto sofferente.

Scenario Clinico (1)

• L'obiettività cardiocircolatoria è negativa: rilevo solo un lieve soffio protosistolico al centrum cordis senza irradiazioni. PA 110/70 mmHg, FC 96/min, ritmica.

• Assenza di rantoli e sibili su tutti i campi polmonari; modesto ↑ della frequenza respiratoria (26-28/min)

• Rassicuro la signora Daniela, ma per l'insistenza del marito, prescrivo visita cardiologica ed ECG urgenti.

• Il cardiologo conferma la mia diagnosi e, per la lieve tachicardia, suggerisce 25 mg di atenololo al mattino.

Scenario Clinico (1)

• Dopo circa un mese, ricevo una telefonata dalla signora Daniela: "non sto bene, i farmaci che assumo non hanno alcun beneficio".

• Invito la signora a venire in ambulatorio, per parlare con calma della sua situazione.

• Il giorno successivo, la signora Daniela si presenta in uno stato di grande prostrazione: è dimagrita, ha il volto scavato, la mimica è molto ridotta e sembra anche un po' trasandata.

Scenario Clinico (1)

• Durante il lungo colloquio la signora riferisce che non sta bene da circa otto mesi, quando è venuta a mancare la sua mamma: ogni giorno si sente sempre più giù di morale, triste e malinconica e le giornate sono sempre più faticose da vivere.

• Riferisce di non avere più interessi: il canto non la stimola più, ed "il pensiero di dover preparare i canti per la prossima Pasqua mi accentua il male alla bocca dello stomaco".

• "Anche al lavoro non ho più stimoli e tutto mi è diventato molto pesante".

Scenario Clinico (1)

• Si accorge anche di trascurare la casa ed i figli e questo le causa un grande senso di colpa. Non prova più nessun piacere nel fare le cose quotidiane, anche il desiderio sessuale e' completamente scomparso.

• Si sente sempre stanca e senza forze fin dal mattino.

• Dopo il lungo colloquio, intuisco che i disturbi della signora Daniela trovano nella diagnosi di depressione la spiegazione più ragionevole.

CLINICAL QUESTIONS

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2. Depressione. Conosciamo solo la punta dell'iceberg?

A. Ritieni ci siano prove sufficienti per attuare, in medicina generale, lo screening dei disordini depressivi dell'adulto?

1. No
2. Sì

U.S. Preventive Services Task Force

Screening for depression. Recommendations and rationale

Ann Intern Med 2002;136:760-4

Screening for depression

- The U.S. Preventive Services Task Force recommends screening adults for depression in clinical practices that have systems in place to assure accurate diagnosis, effective treatment, and follow-up. (grade B recommendation)
- The USPSTF concludes the evidence is insufficient to recommend for or against routine screening of children or adolescents for depression. (grade I recommendation)

Remick RA. CMAJ, 2002

Screening for depression

• The USPSTF found good evidence that screening improves the accurate identification of depressed patients in primary care settings and that treatment of depressed adults identified in primary care settings decreases clinical morbidity.

USPSTF. Ann Intern Med 2002

Screening for depression

• Trials that have directly evaluated the effect of screening on clinical outcomes have shown mixed results.
  - Small benefits have been observed in studies that simply feed back screening results to clinicians.
  - Larger benefits have been observed in studies in which the communication of screening results is coordinated with effective follow-up and treatment.

• The USPSTF concluded the benefits of screening are likely to outweigh any potential harms.

USPSTF. Ann Intern Med 2002

CLINICAL QUESTIONS

?

2. Depressione. Conosciamo solo la punta dell'iceberg?

B. Sei a conoscenza di almeno uno strumento per lo screening della depressione nell'adulto?

1. No
2. Sì, ma non lo utilizzo
3. Sì, e lo utilizzo

Screening for depression

- Beck Depression Inventory
- Center for Epidemiologic Study Depression Screen
- General Health Questionnaire
- Medical Outcomes Study Depression Screen
- Primary Care Evaluation of Mental Disorders
- Symptom-Driven Diagnostic System–Primary Care
- Zung Self-Depression Scale

USPSTF. Ann Intern Med 2002

Screening for depression

Table 1. **Characteristics of Case-Finding Instruments Used To Detect Depression in Adults in Primary Care Settings***

Instrument	Items, nl	Time Frame of Questions	Score Range	Usual Cut-Point†	Literacy Level‡	Administration Time, min
Beck Depression Inventory	21	Today	0–63	Mild, 10; moderate, 20; severe, 30	Easy	5–10
Center for Epidemiologic Study Depression Screen	20	Past week	0–60	16	Easy	5–10
General Health Questionnaire	28	Past few weeks	0–28	4	Easy	5–10
Medical Outcomes Study Depression Screen	8	Past week	0–1	0.06	Average	<2
Primary Care Evaluation of Mental Disorders	2	Past month	0–2	1	Average	<2
Symptom-Driven Diagnostic System–Primary Care	5	Past month	0–1	1	Easy	<2
Zung Self-Depression Scale	20	Recently	25–100	Mild, 50; moderate, 60; severe, 70	Easy	2–5

USPSTF. Ann Intern Med 2002

Why?

Four common clinical errors

1. Insufficient questioning

- Diagnostic failures occur when the patient is not asked questions that may elicit the symptoms of a mood disorder despite what should be a high index of suspicion based on its prevalence.
- The mnemonic “SIGECAPS” (sleep, interest, guilt, energy, concentration, appetite, psychomotor, suicide) may be a useful clinical adjunct (i.e., 4 or more SIGECAPS for major depression, 2 or 3 SIGECAPS for dysthymia).

Remick RA. CMAJ, 2002

Table 1: Diagnostic criteria for major depressive disorder*

A. The patient has depressed mood (e.g., sad or empty feeling) or loss of interest or pleasure most of the time for 2 or more weeks plus 4 or more of the following symptoms

Sleep	Insomnia or hypersomnia nearly every day
Interest	Markedly diminished interest or pleasure in nearly all activities most of the time
Guilt	Excessive or inappropriate feelings of guilt or worthlessness most of the time
Energy	Loss of energy or fatigue most of the time
Concentration	Diminished ability to think or concentrate; indecisiveness most of the time
Appetite	Increase or decrease in appetite
Psychomotor	Observed psychomotor agitation/retardation
Suicide	Recurrent thoughts of death/suicidal ideation

B. The symptoms do not meet criteria for a mixed episode (major depressive episode and manic episode)

C. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

D. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition

E. The symptoms are not better accounted for by bereavement

*Adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.

Remick RA. CMAJ, 2002

Four common clinical errors

2. Failure to consult a family member

- Owing to the cognitive distortions associated with the disease, it is not unusual for patients to minimize or exaggerate their symptoms.
- Thus, in patients who are relatively new to one’s practice, it is risky at best to make (or exclude) a diagnosis of depression without collateral information from a relative, such as a spouse or parent.

Remick RA. CMAJ, 2002

Four common clinical errors

3. Acceptance of a diagnosis of a mood disorder despite lack of diagnostic criteria

4. Exclusion of a diagnosis, or failure to start treatment for depression despite the associated symptom complex

Remick RA. CMAJ, 2002

Decisione clinica (1)

• Prescrivo una terapia a base di:
- paroxetina 20 mg 1 cpr/die al mattino (iniziando con ½ cpr per una settimana)
- alprazolam 0.5 mg (1 cpr alle 8.00 ed una alle 20.00)

• Invito la signora a tornare dopo un mese per un nuovo colloquio.

C. Ritieni appropriata la combinazione di antidepressivi e benzodiazepine nella signora Daniela?

1. No
2. Sì

Furukawa TA, Streiner DL, Young LT.

Antidepressant and benzodiazepine for major depression

The Cochrane Library, Issue 1, 2004. Chichester, UK: John Wiley & Sons, Ltd.

OBJECTIVES

• To determine whether, among adult patients with major depression, adding benzodiazepines to antidepressants brings about any benefit in terms of symptomatic recovery or side-effects in the short term (less than 8 weeks) and long term (more than 2 months), in comparison with treatment by antidepressants alone.

SELECTION CRITERIA

• All RCTs that compared combined antidepressant-benzodiazepine treatment with antidepressant alone for adult patients with major depression.

• Exclusion criteria are: antidepressant dosage lower than 100 mg of imipramine or its equivalent daily and duration of trial shorter than four weeks.

Furukawa TA, et al. Cochrane Library, 2004

MAIN RESULTS

• Nine studies (679 patients)

• The combination group show improvement in their depression (defined as 50% or greater reduction in the depression scale from baseline), within 1 week.

• The difference was no longer significant at 6 to 8 weeks. (none of the included RCTs lasted longer than eight weeks)

• The patients allocated to the combination therapy were less likely to drop out from the treatment due to side effects than those receiving antidepressants alone

Furukawa TA, et al. Cochrane Library, 2004

IMPLICATIONS FOR CLINICAL PRACTICE
• The potential benefits of adding a benzodiazepine to an antidepressant must be balanced judiciously against possible harms including development of dependence and accident proneness, on the one hand, and against continued suffering following no response and drop-out, on the other.

IMPLICATIONS FOR RESEARCH
• We need a long-term, pragmatic RCT to compare the combination therapy (preferably involving two arms, one for continued combination and another withdrawing the benzodiazepine within a month or so) against the monotherapy of antidepressant in major depression

Furukawa TA, et al. Cochrane Library, 2004

CLINICAL QUESTIONS

?

2. Depressione. Conosciamo solo la punta dell'iceberg?

D. Ritieni che i nuovi antidepressivi (SSRI) abbiano un profilo di efficacia/sicurezza nettamente superiore a quello dei triciclici?

1. No
2. Sì

Geddes JR, Freemantle N, Mason J, Eccles MP, Boynton J.

Selective serotonin reuptake inhibitors (SSRIs) versus other antidepressants for depression

The Cochrane Library, Issue 1, 2004.
Chichester, UK: John Wiley & Sons, Ltd.

OBJECTIVES
• To examine the relative efficacy of selective serotonin reuptake inhibitors (SSRIs) compared to other antidepressants

SELECTION CRITERIA
• RCTs comparing SSRI with other kinds of antidepressants in the treatment of patients with depressive disorders.
• The outcome measures assessed included measures of the severity of depression.

Geddes JR, et al. Cochrane Library, 2004

MAIN RESULTS
• Ninety-eight trials contributed data to the analysis of the relative efficacy of SSRIs and related drugs with comparator antidepressants

• Analysis of efficacy was based upon 5044 patients treated with an SSRI or related drug, and 4510 treated with an alternative antidepressant.

Geddes JR, et al. Cochrane Library, 2004

IMPLICATIONS FOR CLINICAL PRACTICE

• There are no clinically significant differences in effectiveness between SSRIs and tricyclic antidepressants in the short-term treatment of depression.

• It is possible that differences may emerge in the longer term

• Treatment decisions need to be based on considerations of relative patient acceptability, toxicity and cost.

Geddes JR, et al. Cochrane Library, 2004

Barbui C, Hotopf M, Freemantle N, et al.

Treatment discontinuation with selective serotonin reuptake inhibitors (SSRIs) versus tricyclic antidepressants (TCAs)

The Cochrane Library, Issue 1, 2004.
Chichester, UK: John Wiley & Sons, Ltd.

OBJECTIVES

• To assess the comparative tolerability of SSRIs and tricyclic/heterocyclic antidepressant drugs.

SELECTION CRITERIA

• Parallel group randomised controlled trials comparing selective serotonin reuptake inhbitors with tricyclic or heterocyclic antidepressants in people with depression.

Geddes JR, et al. Cochrane Library, 2004

MAIN RESULTS

• We included 136 trials.

• The SSRIs showed less participants dropping out compared to the tricyclic/heterocyclic group (odds ratio 1.21, 95% confidence interval 1.12 to 1.30).

• A statistically significant difference was found in total drop-outs between the SSRIs and the old tricyclics as well as the newer tricyclics.

Geddes JR, et al. Cochrane Library, 2004

IMPLICATIONS FOR CLINICAL PRACTICE

• SSRIs shows a, relatively modest, advantage over tricyclic drugs in terms of total drop-outs

• Some pharmaco-economic models may have overestimated the difference of drop-out rates between SSRIs and tricyclic antdepressants (8-12% vs 3% of present systematic review)

• These results are based on short-term RCTs, and may not generalise into clinical practice

Geddes JR, et al. Cochrane Library, 2004

clinical evidence

BMJ Publishing Group

Depressive disorders

Search date July 2002

John Geddes, Rob Butler, and Simon Hatcher

TABLE 1 Adverse events (% of people) with selective serotonin reuptake inhibitors versus tricyclic antidepressants (see text, p 1128).[21]

Adverse effects	SSRI event rates (%)	TCA event rates (%)
Dry mouth	21	55
Constipation	10	22
Dizziness	13	23
Nausea	22	12
Diarrhoea	13	5
Anxiety	13	7
Agitation	14	8
Insomnia	12	7
Nervousness	15	11
Headache	17	14

SSRI, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressants.

Clinical Evidence. March 2004

Trindade E, Menon D.

Selective serotonin reuptake Inhibitors for major depression.

Part I. Evaluation of the clinical literature.

Ottawa: Canadian Coordinating Office for Health Technology Assessment, 1997 August

Table 3: Pooled weighted differences between SSRIs and TCAs in percentages of patients reporting adverse effects*

Category and type of adverse effect	Pooled difference relative to TCAs, %
Adverse effects for which there was no statistically significant difference between any 1 of the 4 SSRIs and all TCAs	
Headache	+2
Tremor	−1
Urinary disturbance	−1
Hypotension	−5

Remick RA. CMAJ, 2002

Table 3: Pooled weighted differences between SSRIs and TCAs in percentages of patients reporting adverse effects*

Category and type of adverse effect	Pooled difference relative to TCAs, %
Adverse effects that occurred statistically significantly more often with TCAs than with at least 1 of the SSRIs	
Dry mouth	29*
Constipation	11*
Dizziness	−9*
Sweating	−3*
Blurred vision	−3*
Palpitations	2

*Adverse event occurred statistically significantly more frequently with an SSRI (positive value) or a TCA (negative value). Based on pooled rate difference obtained by meta-analysis of randomized controlled trials.

Remick RA. CMAJ, 2002

Table 3: Pooled weighted differences between SSRIs and TCAs in percentages of patients reporting adverse effects*

Category and type of adverse effect	Pooled difference relative to TCAs, %
Adverse effects that occurred statistically significantly more often with at least 1 of the SSRIs than with TCAs	
Nausea	+10*
Anorexia	+5*
Diarrhea	+8*
Insomnia	+4*
Nervousness	+4*
Fatigue	−2

Remick RA. CMAJ, 2002

Table 3: Pooled weighted differences between SSRIs and TCAs in percentages of patients reporting adverse effects*

Category and type of adverse effect	Pooled difference relative to TCAs, %
Adverse effects for which there was a statistically significant difference (occurring more often with SSRIs than with the group of TCAs) only for pooled rates	
Agitation	+6*
Anxiety	+5*

Remick RA. CMAJ, 2002

Scenario Clinico (2)

• Dopo un mese, la signora Daniela torna in ambulatorio, ma sia dall'aspetto, sia per sua stessa ammissione, mi accorgo di non aver ottenuto i risultati sperati.

• Anche se lo stato d'ansia è leggermente migliorato, il tono dell'umore è ancora notevolmente depresso.

CLINICAL QUESTIONS

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E. Quale decisione clinica per la signora Daniela?

1. Aumentare il dosaggio della paroxetina
2. Prescrivere un SSRI differente
3. Prescrivere un antidepressivo triciclico
4. Richiedere una consulenza psichiatrica

Non responders patient

• Sixty percent of patients with major depression or a dysthymic disorder will have a clinical response to an adequate trial (3–6 weeks) of an antidepressant.

• However, if there is no response (i.e., no change in SIGECAPS) after 3 weeks, the likelihood of a response is less than 20%,and a switch to an antidepressant of a different chemical class should be contemplated.

Remick RA. CMAJ, 2002

British Association for Psychopharmacology

Evidence-based guidelines for treating depressive disorders with anti-depressants.

March, 2000

Recommendations: Failure to respond

Continue treatment for major depression for at least 4 weeks before considering switching antidepressant due to lack of efficacy (A); extend to 6 weeks in the elderly (D).

Non-response at 4 weeks:

- check adequacy of treatment including dose and non-compliance: increase dose to recommended therapeutic dose if only a low or marginal dose has been achieved (D).
- review diagnosis including possibility of additional physical or psychiatric diagnoses which should be treated in addition (D).
- consider social factors and address if present (D).

BAP. March, 2000

Partial response after 4 weeks adequate treatment in adults: continue treatment with the same antidepressant for another 2 weeks (A).

No response after 4 weeks, or partial response after 6 weeks adequate treatment in adults; recommended options are to:

- increase the dose (C).
- switch treatment to another antidepressant class (C).
- consider a switching to an MAOI in patients with 'atypical' major depression (C).

BAP. March, 2000

Switching antidepressants

• When switching from a TCA to a SSRI, or vice versa, cross-tapering is recommended (i.e. the dosage of the drug to be discontinued is slowly reduced while the new drug is slowly introduced).

• The exceptions are clomipramine, which should not be given with an SSRI, and fluoxetine, which should be stopped before starting a TCA.

• The speed of cross-tapering is best judged by monitoring a person's tolerability. No clear guidelines are available, so caution is required.

Prodigy. April 2003

Switching antidepressants

• When switching between SSRIs, the first SSRI should be withdrawn before the second SSRI is started.

• After stopping fluoxetine, a different SSRI should not be started until 4-7 days later, as it has a long half-life and active metabolites.

• Potential dangers of simultaneously administering two antidepressants include additive effects (e.g. serotonin syndrome, hypotension, drowsiness) and pharmacokinetic interactions (e.g. some SSRIs raise TCA plasma levels).

Prodigy. April 2003

Recommendations: Psychiatric referral

Referral to psychiatric services is indicated if there is a :

- risk of suicide (D).
- psychotic symptoms (D).
- a history of bipolar affective disorder (D).

Consultation with, or referral to, a psychiatrist (or a specialist in the treatment of affective disorders), is appropriate:

- when the practitioner feels insufficiently experienced to manage a patient's condition (D).
- if two or more attempts to treat the patient's depressive disorder have failed or resulted in only partial response (D).

BAP. March, 2000

Decisione Clinica (2)

• Propongo alla signora Daniela una consulenza psichiatrica

• La proposta la spaventò al punto di rifiutare, ma dopo le insistenze, mie e del marito, scelse uno psichiatra del Servizio Igiene Mentale perchè "un parente si era trovato bene".

• Purtroppo, nell'organizzazione del SIMAP dell'AUSL è previsto che i pazienti afferiscano allo "psichiatra competente per territorio" (la città è stata suddivisa in zone ed a ciascuna è stato assegnato uno psichiatra).

Scenario Clinico (3)

• Dopo la visita specialistica, la signora Daniela mi chiese l'approvazione della terapia prescritta:
- Imipramina 25 mg 1 cpr ore 8-12-19
- Alprazolam 0.5 mg una cpr ore 8-13-20.

• Dietro suggerimento dello psichiatra, che aveva consigliato un supporto psicoterapeutico, le indicai una collega di un consultorio privato, che iniziò subito la terapia cognitivo-comportamentale (con frequenza bi-settimanale)

CLINICAL QUESTIONS

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F. Ritieni che, nei pazienti depressi, la terapia cognitivo-comportamentale migliori la risposta terapeutica ai farmaci?

1. No
2. Sì, sempre
3. Sì, solo in particolari circostanze

INTERVENTIONS

Beneficial

Cognitive therapy (in mild to moderate depression) 1132
Continuation treatment with antidepressant drugs (reduces risk of relapse in mild to moderate depression) 1137
Electroconvulsive therapy (in severe depression) 1130
Interpersonal psychotherapy (in mild to moderate depression) 1133
Prescription antidepressant drugs (tricyclic and heterocyclic antidepressants, monoamine oxidase inhibitors, selective serotonin reuptake inhibitors and related drugs) in mild to moderate and severe depression 1125

Likely to be beneficial

Care pathways (in mild to moderate depression) 1129
Combining prescription antidepressant drugs and psychological treatment (in mild to moderate and severe depression) 1134
Non directive counselling (in mild to moderate depression) . . 1133
Problem solving treatment (in mild to moderate depression) . . 1133
St John's Wort (in mild to moderate depression) 1140

Unknown effectiveness

Befriending (in mild to moderate depression) 1137
Bibliotherapy (in mild to moderate depression) 1136
Care pathways versus usual care for long term outcomes (in mild to moderate depression) . . 1138
Cognitive therapy versus antidepressants for long term outcomes (in mild to moderate depression) 1138
Exercise (in mild to moderate depression) 1136
Psychological treatments (cognitive therapy, interpersonal psychotherapy, problem solving treatment) in severe depression 1133

To be covered in future updates

Behaviour therapy

See glossary, p 1139

Clinical Evidence
March 2004

• One non-systematic review of RCTs in people aged 18-80 years has found that, in people with severe depression, adding drug treatment to interpersonal psychotherapy or to cognitive therapy compared with either psychological treatment alone improves symptoms, but found no significant difference in symptoms in people with mild to moderate depression.

• Subsequent RCTs in younger and older adults with mild to moderate depression have found that combining antidepressants plus psychotherapy improves symptoms significantly more than either antidepressants or psychotherapy alone.

Clinical Evidence
March 2004

Scenario Clinico (4)

• Ho rivisto la sig.ra Daniela circa 3-4 settimane fa, dopo sei mesi dalla prima visita psichiatrica

• Riferisce di stare meglio (e si vede!) ed ha ridotto:
- imipramina, 1 cpr 25 mg due volte al dì
- alprazolam, 1 cpr da 0.50 mg due volte al dì
- la frequenza della terapia cognitivo-comportamentale (1 volta la settimana).

• *Last, but not least…*ha ripreso a cantare!