As we have seen, the interplay between chronic pain and psychological symptoms is a delicate and complex matter, but the crossover may allow us to use therapeutic agents that have dual effect, namely on both psychological symptoms such as depression/anxiety and on the purely somatic symptoms.

Furthermore, as in psychiatry, pharmacological strategies are only part of the management, with a multimodal approach being more effective.

This will include measures such as cognitive-behavioural therapy (CBT) as well as medication.

Pharmacological approach:

Briley ([1]) remarked

"Depression is increasingly seen as a triad of psychological, somatic and physical symptoms that all need to be treated to achieve maximal remission,"

noting that the common psychopharmacology between pain and depression suggests that compounds that inhibit the reuptake of both serotonin and norepinephrine are, at least in theory, likely to produce the greatest relief from depression and chronic pain.

Results with trials with members of the new selective serotonin and norepinephrine reuptake inhibitor class of antidepressants (SSNRIs) such as venlafaxine, milnacipran and duloxetine suggest that these compounds may be effective in relieving chronic pain associated with depression or indeed with pain independent of depression.

Allgulander and Kasper ([2]) reported on the use of venlafaxine in conditions such as diabetic neuropathy, fibromyalgia, migraine, premenstrual dysphoric disorder, and stroke, recommending further studies.

Fava et al. ([3]) studied the effects of a new antidepressant, Duloxetine. This has effects on both noradrenaline and serotonin levels.

The authors pointed out,

"Emotional symptoms have been shown to respond to currently available antidepressants; however, physical symptoms may not be as responsive."

Patients receiving Duloxetine, 60 mg q.d.s, exhibited significantly greater improvement than placebo-treated patients in VAS pain measures, approximately 50% of the improvement in overall pain being independent of improvement in Hamilton depression score.

The authors concluded,

"Improvements in pain severity were attributable equally to the direct effect of duloxetine and to associated changes in depression severity. Improvement in painful physical symptoms was associated with higher remission rates even after accounting for improvement in core emotional symptoms."

Goldstein et al. ([4]), also investigating the use of duloxetine, noted,

"Painful physical symptoms are common features of major depressive disorder and may be the presenting complaints in primary care settings."

They evaluated the efficacy of duloxetine in treating emotional and painful physical symptoms in outpatients with major depressive disorder in three randomized, double-blind, placebo-controlled trials.

Compared with placebo, duloxetine was associated with significant reduction in pain severity. The authors concluded that duloxetine reduces the painful physical symptoms of depression.

Papakostas et al. ([5]) investigated somatic symptoms as predictors of time to onset of response to fluoxetine in major depressive disorder.

They found that there was a delayed response to the antidepressant (30% reduction in severity of depressive symptoms as defined using the Hamilton Rating Scale, with 50% reduction at week 8).

A greater number of somatic symptoms at baseline predicted a greater amount of time to onset of clinical response to fluoxetine.

Bupropion has been used in the treatment of anxiety. Fortner et al. also looked at its use to treat depression in elderly patients with medical comorbidity ([6]).

They conducted an 8-week open trial of bupropion SR in patients with major depressive disorder (DSM-IV criteria) and one or more serious medical conditions (e.g. congestive heart failure, diabetes mellitus, irritable bowel syndrome).

Dosing was initiated at 100 mg once daily and increased at weekly intervals to a maximum of 150 mg twice daily as clinically indicated. The mean dose of bupropion SR at endpoint was 222 mg/day, and the drug was relatively well tolerated, with only 2 subjects dropping out due to adverse events and a further 2 for ?other reasons'.

Bupropion SR treatment was associated with reductions in Clinical Global Impressions-Severity

of Illness scale score, Hamilton Rating Scale for Depression (HAM-D) total score, and improvement in QOL (as measured by SF-36).

In particular, the SF-36 "mental health" and "social functioning" domains improved significantly by week 4, whilst "vitality" improved significantly by week 12. On the HAM-D, statistically significant improvement was noted on "depressed mood", "feelings of guilt" , "work and activities", "hypochondriasis" and "insomnia" at week 8.

Anticonvulsant agents such as pregabalin have been found to help reduce anxiety symptoms. The anticonvulsant Gabapentin (GBP), approved by the US Food and Drug Administration (FDA) in 1993 for adjunctive therapy in the treatment of partial seizures, later received approval for the treatment of the neuropathic pain of Post-herpetic neuralgia (PHN) in 2002.

Pregabalin (PGB) is an alpha-2-beta ligand structurally related to GBP, that has analgesic, anxiolytic, and anticonvulsant activity. PGB is currently under review by the FDA as adjunctive therapy for partial seizures, for the management of neuropathic pain associated with diabetic peripheral neuropathy and PHN, and for the treatment of generalized anxiety disorder(GAD) in adults.

A November 2003 study ([7]) reported that PGB (600 mg/day or 300 mg/day depending on creatinine clearance) was safe and effective in the treatment of PHN.
Sabatowski et al. ([8]) recently conducted a randomised, placebo-controlled study which showed that pregabalin(150-300mg a day) reduces pain and improves sleep and mood disturbances in patients with PHN.

At the 2003 23rd Annual Conference of the Anxiety Disorders Association of America, Pollack and colleagues, from the Anxiety Disorders Program, Harvard Medical School, combined data from five studies on the use of various doses of pregabalin in generalized anxiety disorder.

They reported that pregabalin

"shows significant anxiolytic efficacy regardless of the presence of moderately severe comorbid depressive symptomatology. Similarly, [pregabalin] appears to improve depressive symptoms."

Herbal treatment with St. John's Wort is quite common in Germany. Volz et al. ([9]) suggested that this herb may be helpful in somatoform disorders. Using an extract of Hypericum (LI 160) they conducted a trial which resulted in data showing "excellent efficacy and tolerability for LI 160 in somatoform disorders", efficacy being independent of an existing depressive mood.

Compliance, or non-compliance, is frequently a major issue in chronic pain patients. Agosti et al. ([10]) looked at a sample group of nearly a thousand patients drawn from a series of double-blind, placebo-controlled studies of antidepressants (imipramine, phenelelzine, L-deprenyl, mianserin and desipramine).

They found that within the medication group,

"side-effect dropouts had more somatic symptoms than study completers and those who discontinued treatment for miscellaneous reasons."

The findings within the placebo-treated group were not statistically significant, although the authors suggested that they were

"in the same direction as those in the medication group."

The authors remarked,

"Medication discontinuation due to intolerable side-effects remains a significant clinical problem in the treatment of depression."

The same of course applies to chronic pain patients.

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