



Use of Psychotropics and Drug-Drug Interactions in Oncology: Reflections from a Study in a Portuguese Psycho-Oncology Unit

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Abstract

Introduction: Psychopharmacological treatment is an important tool of the multidimensional approach in oncologic setting but cancer patient's susceptibility to drug-drug interactions may pose them at risk.

Objective: To describe the use of psychotropics in patients referred to a psycho-oncology unit and to point out potential and clinical relevant drug-drug interactions in this context.

Methods: Descriptive study of a sample of patients referred for the first time to the Psycho-Oncology Unit of Coimbra University Hospital Centre, between April and December 2013. A retrospective collection of the socio-demographic, clinical and prescription data was made by consulting clinical processes.

Results: From the sample of 110 patients, 51,8% of the patients were already taking some psychotropic drug and 91,9% were on antineoplastic medication at the time of the psycho-oncology appointment. Among the psychotropic medication, almost all were benzodiazepines and antidepressants. Psychotropics can cause potential interactions with antineoplastic medication administered in cancer patients. Some pharmacological agents have more potential to cause drug-drug interactions.

Conclusions: Prescription of psychotropic medication by the oncological team is common and cancer patients usually take several drugs at the same time. This study outlines the importance of promoting scientific research on drug-drug interactions in psycho-oncology and a closer collaboration between oncology and psychiatry in order to reduce the risk of drug-drug interactions, to increase its awareness and to adequately prescribe a psychopharmacologic treatment for each patient.

Keywords: Psychotropic drugs; Psycho-oncology; Drug-drug interactions; Antineoplastic agents

Abbreviations

ADs: Antidepressants; ANs: Antineoplastic Agents; APs: Antipsychotics; BDZ: Benzodiazepines; DDIs: Drug-Drug Interactions; NaSSA: Noradrenergic and Specific Serotonergic Antidepressants; SDRI: Selective Dopamine Reuptake Inhibitor; SSRIs: Selective Serotonin Reuptake Inhibitors; TMX: Tamoxifen

Introduction

Psychotropic medication represents a significant tool in the treatment of psychiatric symptoms or disorders cancer related that affects about half of the cancer patients [1]. Adjustment disorder and major depression are the most frequent in oncology. If undiagnosed and untreated, result in poor quality of life and worst cancer prognosis, which can contribute to exacerbate demoralization syndrome. Furthermore, 80% of the suicides in oncological population are committed by patients with depressive syndrome [2]. Pain, cognitive impairment and acute confusional states are common in advanced states of the disease and also increase risk for suicide [3].

In the last decades, psychopharmacological treatment has been promoted in a multidisciplinary approach to cancer care in order to treat psychiatric disorders and improve cancer patients' quality of life [4]. Advances in psycho-oncology research have also shown the efficacy of psychotropic drugs as adjuvant treatment of cancer-related symptoms, such as pain, hot flushes, pruritus, nausea and vomiting, fatigue, and cognitive impairment [5]. The use of psychotropic medication in cancer patients has been studied in few oncological centres or services. In one of the first reports, data indicated that about half of patients were treated with psychotropic drugs. Hypnotics were

the most frequently prescribed (48%), while antidepressants (ADs) were the least (1%) [6]. Another study reported that antipsychotic (61%) and hypnotics (56%) were the most prescribed drugs and ADs were used in only a minority (10%) [7]. The use of antipsychotics was a lot related to the management of physical symptoms like nausea and vomiting. A later study [8] investigated the use of psychotropic medication in patients referred to a psycho-oncology service and found that over half (55.5%) patients were already on psychotropic drugs at referral, mainly minor tranquilisers (51%) and antidepressants (24%); 22% were on more than one drug; 46% had been prescribed by the oncology team. A more recent study of cancer patients and matched-controls found that the prevalence of emotional distress was higher among cancer patients (15.6% versus 1.4%) and that the volume and duration of psychotropic drug prescriptions was correspondingly higher among cases than controls [9].

Cancer patients are likely to receive psychotropic agents but patients who concurrently receive psychotropic and antineoplastic agents are at high risk of drug-drug interactions (DDIs), which are thought to be

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the cause of approximately 20–30% of all adverse drug reactions [10]. In order to reduce the adverse outcomes of DDIs, potential interactions between anti-cancer drugs and ADs should be identified before these drugs are prescribed and administered in cancer patients.

To our knowledge, this study is the first that sets out to portray the practice in the psychotropic treatment of ambulatory patients referred to a psycho-oncology unit in a large cancer center in Portugal. Recognising the importance of psychopharmacological treatment in cancer patients but also cancer patient’s susceptibility to drug interactions, the aims of our study were to describe the use of psychotropic medication in patients referred to a psycho-oncology unit and to point out potential and clinical relevant drug-drug interactions in this clinical context.

Material and Methods

Patients referred for the first time to the psycho-oncology unit of the oncology day-hospital from Coimbra University Hospital Centre over a 9-month period, from of April to December 2013 were selected. This psycho-oncology unit only admitted cancer outpatients receiving oncological treatment at the oncology day-hospital and who were attending the oncology consultation at the moment of the psychiatric assessment. A descriptive and retrospective study was elaborated by consulting hospital records for each patient. Socio-demographic, clinical and therapeutic data were collected.

Results

A total of 110 oncological patients were referred to the psycho-oncology consultation during the 9-month period. Main demographic and clinical characteristics of the sample are shown in Table 1.

The most common causes for psychiatric assessment were addressed by the oncology team as ‘depressive symptoms’, ‘anxiety’, ‘emotional problems’ and ‘insomnia’. In this sample, 51,8% of the patients were already taking some psychotropic medication at the time of the psycho-oncology appointment (Table 2). Drugs were most prescribed by the oncologist or another physician of the oncology team (80,6%). Among the psychotropic medication, almost all were anxiolytics (benzodiazepines) and/or ADs. With respect to the first class of the two pharmacological agents, short acting benzodiazepines (especially alprazolam and lorazepam) were the most prescribed; in the case of antidepressants, selective serotonin reuptake inhibitors (SSRIs), especially sertraline and paroxetine, were the most common physician’s option. Following psychiatric assessment, the most common psychiatric diagnoses were adjustment disorder (58,6%) and depressive disorder (41,4%). In addition, some pharmacotherapeutic change occurred for the majority of patients, particularly with the introduction of an antidepressant, the increasing dosage of the antidepressant, drug discontinuation or the switch to a different pharmacological agent. Regarding oncological treatment, almost all patients (91,9%) were on chemotherapy cancer treatment and antineoplastic agents (ANs) used by the patients are listed on Table 3.

Discussion

The result that almost half patients referred to psycho-oncology unit had metastatic disease and received cancer diagnosis by one year is congruent to what has been reported by some studies. It seems that there is a tendency to prescribe psychotropic medications and/or refer patients to liaison psychiatry or psycho-oncology in the advanced phase or even palliative phase of cancer, as physical and psychological symptoms get worse and physicians feel they have no more to offer to their patients [11,12].

Psychiatric assessment was requested mainly because psychological distress and psychopathology was noted by physicians from the oncology team, which is a positive finding suggesting awareness about psychological/psychiatric morbidity. Our study found that more than half of patients were already taking some psychotropic medication at the psycho-oncology appointment, which is higher than the one found in other studies [6-8] and suggests that pharmacotherapy is being an increasingly intervention tool.

After psychiatric assessment, increasing the dosage or switching to another drug where the most frequent changes. In fact, correct use of psychotropic medication demands a careful evaluation, particularly concerning patient’s physical condition, clinical and psychiatric symptoms, drug-drug interactions and side effects.

Antidepressants

In our work we found a quite higher percentage (59,6%) of antidepressant use compared to what was reported by previous studies [6-8]. This might be related to many factors: more awareness to psychological distress from the oncological team; the development of new classes of ADs with a better tolerability and safety profiles; increasing scientific evidence showing that ADs, irrespective of their class, are more effective than placebo in treating depression in cancer patients [13]. Also the fact that recent ADs with sedative and increasing appetite properties, like mirtazapine, are useful and adequate to manage the sleep disturbance and anorexia, which are common symptoms in cancer patients [14,15]. Somnolence, hyperphagia and weight gain side effects may be attributed in part to the antihistaminic activity of mirtazapine at low doses.

Number of patients, n	110
Gender (%)	
Female	59,1
Male	40,9
Age (years)	
Mean	54
Min-Max	23-82
Civil status (%)	
Single	13,6
Married	69,1
Widow	11,8
Divorced	5,5
Cancer type (%)	
Gastro-intestinal	24,5
Breast	20,9
Lung	17,3
Hematological	12,7
Gynecological	8,2
Brain	4,5
Other	11,8
Clinical Stage (%)	
Advanced/metastatic	47,3
Local	52,7
Diagnosis date (%)	
>1 year	40,9
<1 year	59,1
Past psychiatric history (%)	
Yes	13,6
No	86,4

Table 1: Demographic and clinical characteristics of patients.

Patients taking psychotropics (%)	51,8
Anxiolytics (%)	90,5
Alprazolam	
Lorazepam	
Other	
Antidepressants (%)	59,6
SSRI	
NaSSA	
SDRI	
Other	
Antipsychotics (%)	8,2

Table 2: Psychotropic drugs before referral.

Alkylating agents	Cyclophosphamide, Temozolomide	Procarbazine,
Antimetabolites	Capecitabine, Cytarabine, Methotrexate, Pemetrexed	Fluorouracil,
Antimicrotubules	Docetaxel, Vinblastine, Vincristine	
Hormone agonists/antagonists	Anastrozole, Goserelin, Leuprolide, Octreotide, Tamoxifen	Cyproterone, Fulvestrant,
Platinum compounds	Cisplatin, Carboplatin, Oxaliplatin	
Topoisomerase inhibitors	Doxorubicin, Epirubicin, Irinotecan	Etoposide,
Tyrosine kinase inhibitors and monoclonal antibodies	Bevacizumab, Rituximab, Trastuzumab	Bortezomib, Erlotinib,

Table 3: Antineoplastic agents used by the patients on chemotherapy treatment.

Psycho-oncology research indicates that ADs should be reserved for patients with clinical depression, moderate or severe in intensity, otherwise their use does not appear to have any significant benefit over placebo [16], and cancer patients with depressive-like symptoms as part of an adjustment disorder seem to respond weakly to ADs [17].

Among the new classes of ADs there are the serotonin reuptake inhibitors (SSRIs) (e.g., fluoxetine, paroxetine, sertraline, citalopram and escitalopram), selective serotonin and noradrenergic reuptake inhibitors (SNRIs) (e.g. venlafaxine, duloxetine), selective noradrenergic and dopamine reuptake inhibitors (NDRIs) (e.g., bupropion), and noradrenergic and specific serotonergic antidepressants (NaSSA) (e.g., mirtazapine). In our study the most prescribed ADs were sertraline, paroxetine and mirtazapine, which represent common psychopharmacologic options that have shown their efficacy in cancer patients, according to data of non-randomised controlled trials [18,19]. Although a better tolerability and safety profiles of these new classes of ADs might have contributed to their increasing prescription by non-psychiatrist in the last decades, the risk of inadequate or unnecessary ADs prescription should be taken into account, especially in cases of high potential for drug interactions. Generally, anti-cancer drugs and ADs can interact through pharmacokinetic or pharmacodynamic mechanisms [10]. Pharmacokinetic interactions are mainly a result of inhibition or induction of the cytochrome P450 (CYP450) isozymes, since ADs are metabolized through the cytochrome P450 enzyme system (CYP450). Pharmacodynamic interactions occur when the concurrent use of two drugs results in an alteration of the therapeutic and/or toxic effects of either drug without altering their pharmacokinetics. These

interactions can be additive, synergistic or antagonistic [10].

DDIs can result in clinically significant changes in pharmacokinetics and/or pharmacodynamics of antineoplastic agents (ANs) altering their therapeutic efficacy and toxicity. Both ADs and ANs have narrow therapeutic indices and consequently, small variations in their plasmatic concentrations may result in sub-therapeutic or toxic effects [20]. The literature is scarce on reviews or research addressing the drug interactions between ANs and ADs and their clinical consequences and the majority of information available comes from animal experiments or in vitro tests. The pharmacokinetic drug interactions with ADs are unlikely with busulfan, chlorambucil, estramustine, mechlorethamine, melphalan, temozolomide, 5-fluorouracil, gemcitabine, mercaptopurine, thioguanine, cisplatin, carboplatin, oxaliplatin, daunorubicin, doxorubicin, doxorubicin, epirubicin and vorinostat. Among the remaining ANs, the risk of loss of efficacy or increased toxicity, when coadministered with certain ADs, is a possibility [20]. Most of them are subjected to metabolism by CYP 450 3A4 should be used with caution concomitantly with inhibitors of this isoenzyme such as fluoxetine, sertraline, paroxetine and fluvoxamine. Fluvoxamine is a CYP3A4 inhibitor and therefore has many DDIs with ANs such as: doxorubicin and etoposide, both susceptible to pharmacokinetic interactions involving competitive CYP3A4 inhibition; cyclophosphamide and ifosfamide, both major substrates of CYP3A4; docetaxel and paclitaxel, both substrates of CYP3A4 and therefore, interactions that involve ADs which inhibit this isozyme [21]. Precautions should be employed when using irinotecan and ADs in colon cancer patients. Irinotecan has significant pharmacodynamic and pharmacokinetic interactions and drugs acting on the serotonergic system (e.g. desipramine, paroxetine, and sertraline) which are inhibitors of CYP2B6 may increase the levels/effects of irinotecan [22]. Cyclophosphamide and ifosfamide are inhibitors of CYP2B6, and can theoretically decrease the clearance of bupropion, a dopamine reuptake inhibitor which is a major substrate of the same isoenzyme. Co-administration of bupropion with these ADs can potentially affect the clinical activity of bupropion [21]. Escitalopram, citalopram, venlafaxine, mirtazapine and milnacipram are ADs with minimal CYP 450 inhibitory potential and are therefore seems safer in these patients [20].

Tamoxifen (TMX) has been very studied for drug interactions with ADs and results point that drugs that inhibit CYP 2D6 can reduce the clinical benefit of TMX and SSRIs inhibit, to varying degrees, CYP 2D6 [20]. Certain SSRIs such as paroxetine and fluoxetine can interact most with TMX by strongly decreasing the levels of its active metabolites. Venlafaxine, mirtazapine, citalopram and escitalopram are small inhibitors of CYP 2D6, therefore being a safe choice when using TMX [20].

Benzodiazepines anxiolytics

The high rate of benzodiazepines (BDZ) anxiolytics use is similar to previous studies and it has been shown for many years to be useful for anxiety and emotional distress [23,24]. Most BDZ are metabolized by CYP P450 and possess potential for DDIs with other drugs. Alprazolam was one of the most frequent BDZ option in our study. It has significant potential for DDIs because cytochrome P450 3A (CYP 3A) metabolizes this drug, rendering sensitive to a wide array of CYP 3A inhibitors and inducers. Among CYP 3A inducers, there is dexamethasone, common in oncological practice. Because of the pharmacologic complexity of many cancer treatment regimens, anxiolytics with fewer interactions such as BDZ which are metabolized through glucuronidation (e.g., lorazepam, oxazepam) are preferable in this setting [25].

Midazolam has been used in the treatment of cancer related symptoms especially in the terminal phase of the disease, including extreme anxiety, pain, dyspnoea, nausea, restlessness, and agitated delirium. Tyrosine kinase inhibitors (e.g., erlotinib and gefitinib) have also been shown to interact with midazolam based on in vitro and substrate binding studies, possibly due to induction of CYP3A4 by the ANs [10]. Midazolam is a substrate of this isozyme, and pretreatment and co-administration with erlotinib was shown to decrease the total exposure to midazolam in a small open-label study of 16 cancer patients [10].

Antipsychotics

The use of antipsychotics (APs) in our sample was lower compared to the results obtained in the last decades, when typical antipsychotics, also called neuroleptics (e.g., haloperidol, prochlorperazine) have been used for the management of cancer-related symptoms (e.g., nausea and vomiting) for more than 30 years. Both haloperidol (a butyrophenone) and prochlorperazine (a phenothiazine) block D2 receptors found in the chemoreceptor trigger zone, but haloperidol is a more potent and pure D2 receptor blocker.

In more recent years, second generation antipsychotics (e.g., olanzapine, quetiapine, risperidone), also known as atypical APs, have been used in psycho-oncology in the treatment of delirium, as well as of medical symptoms and chemotherapy side effects in patients with cancer. APs are metabolized via the CYP450 system (especially CYP1A2, CYP2D6, and CYP3A4) with possible interaction with other medications that by inhibiting CYP450 enzymes or by inducing their activity may increase or reduce, respectively, plasma levels of APs. Concomitant administrations of antipsychotics in patients who are on anthracycline therapy (e.g., doxorubicin, epirubicin) may predispose them to increased risks of drug-induced QT prolongations and torsades. Antipsychotic related haematological disorders (neutropenia, aplastic anaemia, thrombocytopenia, and rarely agranulocytosis), observed with clozapine and some other atypical APs must be taken into account especially for myelo-suppressed patients [26].

Our study has several limitations, both the sample size and the unicentric methodology used compromises the external validity of the study. The use of descriptive statistical methods limits the projection of the conclusions. The discussion about DDIs in oncology did not intend to be exhaustive, but to point out potential DDIs that may be clinically important in cancer patients.

Conclusion

The use of psychotropic medication by oncologists in patients referred to psychiatric assessment is common. Psychopharmacological treatment represents some of the main challenges for the future of multicomponent interventions in psycho-oncology but cancer patients are a physically vulnerable population, usually, taking several drugs and, therefore, in particular risk of drug interactions.

This study outlines the importance of promoting scientific research on drug-drug interactions in psycho-oncology and a closer collaboration between oncology and psychiatry in order to reduce the risk of DDIs, to increase its awareness and to adequately prescribe a psychopharmacologic treatment for each patient.

References

1. Pasquini M, Biondi M, Costantini A, Cairoli F, Ferrarese G et al. (2006)

Detection and treatment of depressive and anxiety disorders among cancer patients: Feasibility and preliminar findings from a Liaison Service in an Oncology division. *Depress Anxiety* 23: 441-448.

2. Henriksson MM, Isometsa ET, Hietanen PS, Aroa HM, Lönnqvist JK (1995) Mental disorders in cancer suicides. *Journal of Affective Disorders* 36: 11-21.

3. Breitbart W, Gibson C, Abbey J (2006) Suicide in palliative care. *Textbook of palliative medicine*. London: Hodder Arnold 860-868.

4. Okamura M, Akizuki N, Nakano T, Shimizu K, Ito T, et al. (2008) Clinical experience of the use of a pharmacological treatment algorithm for major depressive disorder in patients with advanced cancer. *Psychooncology* 17: 154-160.

5. Thekdi SM, Irarrazaval ME, Dunn L, Luigi Grassi, Michelle Rib (2012) Psychopharmacological Interventions. *Clinical Psycho-Oncology: An International Perspective*. Wiley-Blackwell 109-126.

6. Derogatis LR, Feldstein M, Morrow G, Schmale A, Schmitt M, et al. (1979) A survey of psychotropic drug prescriptions in an oncology population. *Cancer* 44: 1919-1929.

7. Jaeger H, Morrow GR, Carpenter PJ, Brescia F (1985) A survey of psychotropic drug utilization by patients with advanced neoplastic disease. *Gen Hosp Psychiatry* 7: 353-360.

8. Cullivan R, Crown J, Walsh N (1998) The use of psychotropic medication in patients referred to a psycho-oncology service. *Psychooncology* 7: 301-306.

9. Desplenter F, Bond C, Watson M, Burton C, Murchie P, et al. (2012) Incidence and drug treatment of emotional distress after cancer diagnosis: A matched primary care case-control study. *Br J Cancer* 107: 1644 - 1651.

10. Yap KYL, Tay WL, Chui WK, Chan A (2011) Clinically relevant drug interactions between anticancer drugs and psychotropic agents. *Eur J Cancer Care* 20: 6-32.

11. Farriols C, Ferrández O, Planas J, Ortiz P, Mojal S, et al. (2012) Changes in the prescription of psychotropic drugs in the palliative care of advanced cancer patients over a seven-year period. *J Pain Symptom Manage* 43: 945-952.

12. Ng CG, Boks MP, Zainal NZ, Wit NJ (2011) The prevalence and pharmacotherapy of depression in cancer patients. *J Affect Disord* 131: 1-7.

13. Laoutidis ZG, Mathiak K (2013) Antidepressants in the treatment of depression/depressive symptoms in cancer patients: A systematic review and meta-analysis. *BMC Psychiatry* 13: 140.

14. Riechelmann RP, Burman D, Tannock IF (2010) Phase II trial of mirtazapine for cancer-related cachexia and anorexia. *Am J Hosp Palliat Care* 27: 106-10.

15. Savard J, Morin CM (2001) Insomnia in the context of cancer: A review of a neglected problem. *J Clin Oncol* 19: 895-908.

16. Stockler MR, O'Connell R, Nowak AK, Goldstein D, Turner J, et al. (2007) Zolof's Effects on Symptoms and Survival Time Trial Group. Effect of sertraline on symptoms and survival in patients with advanced cancer, but without major depression: A placebo-controlled double-blind randomised trial. *Lancet Oncol* 8: 603-612.

17. Hart SL, Hoyt MA, Diefenbach M, Anderson DR, Kilbourn KM, et al. (2012) Meta-analysis of efficacy of interventions for elevated depressive symptoms in adults diagnosed with cancer. *J Natl Cancer Inst* 104: 990-1004.

18. Torta R, Siri I, Caldera P (2008) Sertraline effectiveness and safety in depressed oncological patients. *Supportive Care in Cancer* 16: 83-91.

19. Cankurtaran ES, Ozalp E, Soygur H, Akbiyik DI, Turhan L, et al. (2008) Mirtazapine improves sleep and lowers anxiety and depression in cancer patients: Superiority over imipramine. *Supportive Care in Cancer* 16: 1291-1298.

20. Miguel C, Albuquerque E (2011) Drug interaction in psycho-oncology: Antidepressants and antineoplastics. *Pharmacology* 88: 333-339.

21. Chan A, Rong DNT, Yap KYL (2012) Clinically relevant anticancer antidepressant drug interactions. *Expert Opin Drug Metab Toxicol* 8:173-199.

22. Di Paolo A, Bocci G, Polillo M, Del Re M, Di Desidero T, et al. (2012) Pharmacokinetic and pharmacogenetic predictive markers of irinotecan activity and toxicity. *Curr Drug Metab* 12: 932-943.

23. Tsavaris N, Kosmas C, Vadiaka M, Sougioultzis S, Kontos A, et al. (2001) Comparative study of tropisetron with the addition of dexamethasone or

- alprazolam in breast cancer patients receiving adjuvant chemotherapy with CEF (cyclophosphamide, epirubicin and 5-fluorouracil). *J Chemother* 13: 641-647.
24. Roscoe JA, Morrow GR, Aapro MS, Molassiotis A, Olver I, et al. (2011) Anticipatory nausea and vomiting. *Supportive Care in Cancer* 19: 1533-1538.
25. Ilana M, William E (2010) *Psychotropic Medication in Cancer Care*. Oxford University Press.
26. Nooijen PM, Carvalho F, Flanagan RJ (2011) Haematological toxicity of clozapine and some other drugs used in psychiatry. *Hum Psychopharmacol* 26: 112-119.