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Editorial

Stem Cell Therapy: Future of Pain Medicine

YiLi Zhou, Bohdan Warycha, and Hoang Vu

Nearly 30% of seniors have chronic musculoskeletal pain. The most common cause of pain in seniors is related to the degenerative changes of the spine and joints[9]. Conventional treatments are often restricted to the management of symptoms. Use of chronic anti-inflammatory medications in seniors may bear serious risks in gastrointestinal and renal systems. Physical therapy has limited value. Epidural steroid injection(s) may provide up to three months of pain relief. However, there are some risks involved. Spine surgery for degenerative spine diseases has a limited success rate. Up to 30% or 40% of patients may continue to have pain after back surgery. Surgical repair of a knee injury and knee replacement surgeries are popular. However, the costs are relatively high. Many senior patients may not be ideal candidates for surgery due to cardiovascular conditions. Furthermore, all these treatments do not address the key cause of spine and joint pain due to degeneration of cells and subsequent tissue damage[9]. Recent development in stem cells therapy (SCT) has provided a new hope for seniors.

Back Pain

The major cause of back pain is the degeneration of the cells in the intervertebral discs. Over the last few years molecular, cell-based therapies and tissue-engineering strategies with SCT for disc regeneration have significantly increased. A recent report showed that injection of mesenchymal stem cells (MSC) into bovine intervertebral discs can increase the expression of extracellular type II collagen and maximize extracellular matrix production[7]. Chun et al [1]injected human adipose-derived stem cells (ADSCs) into 20 mature male New Zealand white rabbits. The proliferation of ADSCs at the L4-5 disc was found at 10 weeks after cell injection. Histologically, the ADSC-injected discs exhibited elevated extracellular matrix secretion and little ossification of damaged cartilage in the nucleus pulposus compared with degenerative control discs.

In addition to the promising results from animal research, preliminary human studies showed mixed results. In 2006, Haufe et al[3] reported 10 patients who underwent intradiscal injection of hematopoietic precursor stem cells (HSCs) obtained from their pelvic bone marrow. Of the 10 patients, none achieved any improvement of their discogenic low back pain after one year follow-up. More recently Orozco et al [8] reported a study of ten patients with chronic back pain treated with intradiscal injection of autologous expanded bone marrow MSC. Patients were followed for 1 year. Rapid improvements of pain and disability were reported (85% of maximum in 3 months). Although disc height was not recovered, water content was significantly elevated at 12 months. Advantages of intradiscal MSC therapy include simpler and preservation of normal biomechanics without surgery. However, long term survival of the transplanted MSCs in the harsh environment of the discs is still a major challenge. To the date, no double-blind, controlled studies have been published to confirm the clinical efficacy of SCT for the pain due to degenerative disc diseases.

Knee Pain

It is estimated there will be seven-fold increase in knee replacements in the United States between 2005 and 2030. However, SCT may reduce the future need for knee replacement[5]. Autologous MSC and ex vivo expanded skeletal SC all have shown promising results in the treatment of knee pain caused by osteoarthritis (OA).

In an experimental animal meniscus injury model, it has been reported [10] that transplantation of human meniscus stem/progenitor cells (hMeSPCs) effectively protected articular cartilage, promoted neo-tissue formation with better-defined shape and more matured extracellular matrix and smother surface cartilage, and maintained joint space at 12 weeks postsurgery[11]. MSC therapy may also reduce animal pain behavior[14].

In human studies, Turajane et al[13] conducted a case-series study with five patients that failed conservative treatment. It was reported that the combination of intra-articular autologous activated peripheral blood stem cells with growth factor addition/preservation along with hyaluronic acid in conjunction with arthroscopic microdrilling MCS resulted in Quality of Life improvements and succeeded in regenerating articular cartilage in early osteoarthritic knee disease. Skowronski[12]reported 52 patients treated with autologous blood MSC for knee pain due to cartilage lesions. Scores improved across all scales with an average improvement of 23 points in the Knee Injury and

Osteoarthritis Outcome Score scale and 35 points in the Lysholm knee scale at one year.

Koh et al[4] treated eighteen patients with injection of autologous fat pad-derived MSC for knee pain due to OA. Patients were followed for 24 to 26 months after therapy. Western Ontario and McMaster Universities Osteoarthritis Index, Lyholm scores as well as VAS scores all significantly improved. Radiographic study showed the whole-organ MRI score had significantly improved from 60.0 points to 48.3 points at the final follow-up point. Particularly notable was the change in cartilage whole-organ MRI score, which improved from 28.3 points to 21.7 points. More recently, Vangsness et al reported[15]a randomized, double-blind, controlled study on adult human MSC delivered via intra-articular injection to the knee following partial medial meniscectomy. A single superolateral knee injection was given to 55 patients within seven to ten days after the meniscectomy. It was found that there was significantly increased meniscal volume determined by quantitative MRI in groups that received SCT. No patients in the control group had significant increase in meniscal volume. Patients with osteoarthritic changes who received MSC experienced a significant reduction in pain compared with those who received the control. This randomized, double-blind, controlled study confirmed that MSC could be a promising treatment for knee pain due to osteoarthritis and meniscus tear.

Challenges for SCT

The advantage of SCT is that stem cells can regenerate healthy and functionally specialized cells and tissues to replace the destroyed or degenerative tissues. Though it is promising, it is still facing a variety of challenges. Firstly, there are many studies reporting the clinical efficacy, most studies are open label. Only few, if any, double-blind, controlled studies have supported the efficacy of SCT for knee pain due to osteoarthritis. To the date, there are no controlled studies confirming the clinical efficacy of SCT for degenerative spine diseases. Thus more clinical studies are needed. Secondly, biological techniques for stem cell transplantation are waiting to be enhanced. For example, the stem cells transplanted into degenerated intervertebral discs will face a harsh environment, which has very high pressure, low nutrition and low oxygen. To enhance the cell survival rate and ensure the transplanted cells differentiating toward chondrocyte-like cells, which can produce proteoglycans and type II collagen, more basic science studies are needed[2]. The third challenge for SCT is iatrogenic cancerogenesis. Embryonic stem cells, including totipotent stem cells (produced from fusion of egg and sperm), and pluripotent stem cells (5-14 day old blastocytes) have a strong potency of cell reproducing and potentially highly teratogenic. Novel strategies such as using transgenic expression of the genetically engineered human recombinant DNases in proliferating and directed differentiation resisting stem cells are being developed to inhibit or prevent the iatrogenic cancerogenesis[6]. Adult SCs (Adipose, peripheral and bone marrow derived SCs) have the ability to differentiate and form a variety of tissues. These adult SCs have been used in researches to treat variety of human diseases. So far no iatrogenic carcinomas have been reported as the results of the treatment. The fourth major issue related to SCT is the legal challenge. Worldwide, different countries have different laws on SC research and use. Even President Barack Obama signed an executive order on March 9, 2009 to lift the restrictions on federally funded human embryonic stem cells (hESC) research, currently only adult stem cells (adipose, peripheral and bone marrow derived stem cells) are allowed to be used in most clinical settings. These cells should be minimally manipulated. Use of hESC from fetus, umbilical cord and amniotic fluid are all limited for research purposes. Researchers and clinicians must be familiar with the laws of their respective countries and states before becoming involved in SC therapy or research.

Conclusion

The treatment of chronic pain conditions is constantly evolving. Recent advancements in SCT for pain due to degenerative diseases in the spine and joints are promising and indicative that SCT will undoubtedly play a major role in the future. However, more studies are needed to enhance the biological techniques, confirm the clinical efficacy, reduce the risk of iatrogenic carcinoma and address the legal issues related to this exciting treatment. It is likely that SCT will be utilized more extensively in the future for replacing diseased tissues as an alternative to open back surgery or joint replacement.

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Competing Interests
None
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Research Article

Effectiveness of cognitive behavioural psychotherapy alone and combined with pharmacotherapy in binge eating disorder: a differential research.

Lanzarone Cristina, Cuzzocrea Francesca, Larcan Rosalba, Bongiorno Antonio and Minì Valentina

Abstract

Objective: This research aimed to verify the differences between patients with Binge Eating Disorder (BED) treated with Cognitive Behavioural Therapy (CBT) alone and those treated with CBT in combination with medication.

Method: A selection of 30 subjects affected by BED was carried out on the basis of experimental outcomes that evidenced the efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs) in the treatment of obesity associated with BED. Some participants underwent CBT alone while the others, in addition to CBT, were treated with bio-equivalent doses of either Paroxetine or Venlafaxine. Binge eating behaviour, impulse regulation, different features of eating behaviour (restrained eating, uncontrolled eating and emotional eating) and different psychotic conditions (Psychopathic Deviate, Depression and Hypomania) were studied during pre- and post-treatment phases. Both the psychological (CBT) and the pharmacological (CBT + SSRIs/SNRIs) therapies were assessed in keeping with the parameters examined.

Results: The data showed that CBT alone seems to favour a greater reduction in depression and hypomania as well as the subject's ability to control eating behaviour; whereas pharmacological treatment appears to control primarily the impulsiveness of food intake.

Keywords: Eating Behaviours, Bing Eating Disorder, Personality, Cognitive-Behavioural Therapy, Pharmacotherapy

Introduction

Binge Eating Disorder (BED) was first defined by Stunkard in 1959[1]; he identified peculiar food intake features characterized by a loss of control in a subgroup of obese patients. Various efforts have been made, ever since, to provide a non-sociological approach to individuals with such a behaviour disorder, which has long been considered a variant of Bulimia Nervosa.

Unlike patients affected by Bulimia Nervosa, patients with BED appear to be overweight and mainly obese. Thus, the treatment aims not only at reducing BED and its related psychopathology, but also at assessing the weight gain experienced by these patients to prevent a further worsening of physical health.

Walsh & Devlin[2] evaluated the use of medication in the treatment of Bulimia Nervosa and BED, underlining the efficacy of antidepressant medication in the treatment of Bulimia Nervosa. The antidepressant efficacy led to consider its use in BED more accurately.

Williamson, Martin & Stewart[3] stated that pharmacotherapy was not an effective treatment for Anorexia Nervosa. However, it did prove to be successful in Bulimia Nervosa and BED, although subjects affected with eating disorders apparently respond better to psychotherapy approaches.

Systematic investigations have been conducted on the aetiology of BED. Biological and genetic factors, neurotransmitters and hormones have been involved in the onset of binge eating and play an important role in the regulation of hunger and mood.[4, 5] However, a definitive aetiological theory has not been developed and tested.[3]

BED is characterized by a relevant psychological component that in many cases is under-evaluated. Patients with BED have difficulty in interpreting the visceral sensations of hunger and satiety; they take large amounts of food even during regular meals and, moreover, their food contains more fat than protein.[6, 7]

In fact, Axis I and II disorders (DSM IV-TR) share common features with binge eating.[8] Axis I psychiatric disorders (including depression, anxiety, body dysmorphic disorder, or chemical addiction) characterize many BED patients, and research has evidenced the presence of panic, loss of control, impulsivity, compulsive behavior, obsessive thoughts about food and social phobia.[9] Axis II personality disorders (especially borderline personality disorder) are frequently related to patients suffering from eating disorder and comorbidity with Avoidant Personality Disorder and Obsessive-Compulsive Disorder was observed.[10]

BED is not associated with a restrained eating control, but probably with an increase of uncontrolled eating and emotional eating.[11, 12]

Pharmacological agents, compared to placebo, have been used in the treatment of BED. Appolinario, Bacaltuchuk, Sichieri et al[13] evaluated the efficacy of Sibutramine to reduce the frequency of binge eating, while McElroy, Arnold, Shapira et al[14]focused on Topiramate and evidenced a greater reduction in binge eating frequency but with side effects such as paraesthesia.

Other studies showed the efficacy of Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Noradrenaline Reuptake Inhibitors (SNRIs) in the treatment of obesity associated with BED[15, 16, 17, 18] showing that SSRIs and Tricyclic Antidepressants (TCAs) reduced the frequency of BED compared to placebo.[19] To determine which patients are most likely to benefit from medications, and how to sequence the various therapeutic interventions available better, are questions still open to debate.

Moreover, results in many cases appear to be divergent. Ciao, Latner and Durso[20] underlined the influences of other factors that may influence treatment efficacy. They observed that many obese individuals who might benefit from weight loss treatment nevertheless do not plan or desire to seek treatment and perceive multiple barriers to treatments.

Pharmacotherapy may enhance weight loss,[19] although other results suggest that pharmacotherapy may be associated with a reduction in binge frequency in obese patients with BED, but it does not lead necessarily to weight reduction.[21] These medical treatments seem to be effective in reducing binge frequency over the short-term, and the subsequent discontinuation of the medication seems to be associated with a relapse of binge eating. Thus further studies of the role of pharmacotherapy in the treatment of BED need to be carried on.[22]

According to Williamson, Martin and Stewart[3] the additive effects of psychotherapy, e.g. Cognitive Behavioural Therapy (CBT), and pharmacotherapy have to be investigated. At present it seems that adding pharmacotherapy to psychotherapy does not help to reduce binge frequency compared to psychotherapy alone.

The efficacy of CBT has been substantiated by scientific literature[23, 24, 25, 26] and *Vaidya*[27] *stating that* CBT helps patients reduce eating disorder habits by making them aware of the cause of their self-sabotage, while affecting weight indirectly.

Psychotherapy treatment over a one-year period deals with binge symptoms and aims at reducing the possibility of relapse by gathering different techniques for the maintenance of long-term results through the use of specific individual intervention protocols. The main target of the intervention is to facilitate the management of no-control food intake episodes and of impulsivity through the alteration of behaviour, and of cognitive and emotional factors related to eating disorders.

Thus, the main objective of this research was to verify the possible differences between those subjects with BED who underwent psychotherapy combined with pharmacotherapy and those who underwent psychotherapy only. In particular, it aimed at verifying possible differences between the various therapeutic strategies on eating behaviour (restrained eating, uncontrolled eating and emotional eating) and the behavioural and psychopathological features (psychopathic deviate, depression and hypomania).

The main hypothesis was to determine if patients who underwent CBT and pharmacotherapy with bio-equivalent doses of the SSRI Paroxetine or SNRI Venlafaxine obtained a considerable benefit from the pharmacotherapy on impulse regulation, on eating behavior and on personality features compared to those who underwent CBT alone.

The second hypothesis was to verify if Paroxetine and Venlafaxine treatments were equally effective on impulse regulation, eating behavior and on personality characteristics.

Methodology

Participants

A group of 30 subjects with BED were selected. All these subjects applied for support to the Inter-Service-Psychology Clinic for Eating Disorders and they were assisted by a Cognitive Behavioural Therapist. They were all of Italian nationality, aged 22 to 52, with a Body Mass Index (BMI) range of 26 to 35. All participants belonged to a middle class socio-cultural level. They were informed of the objectives of the research and signed a consent form. Those subjects who were diagnosed with binge eating less than two years ago, those aged over 65, or those who were suffering from other debilitating or chronic diseases were preliminarily excluded from this research.

Measures and procedure

Participants were recruited according to the nature of the assessments. More specifically, assessments had to address the effect of psychotherapy and pharmacotherapy in subjects with BED on their impulse regulation, their eating behavior (restrained eating, uncontrolled eating and emotional eating), and their personality features (Psychopathic Deviate, Depression and Hypomania). The 30 subjects selected were randomly assigned to three different treatments. Ten subjects had only CBT, ten subjects underwent psychotherapy with Paroxetine, and ten subjects underwent psychotherapy with Venlafaxine.

Each participant answered questionnaires during the assessment phase and in the post-training phase (after one year of psychotherapy). More specifically:

Binge Eating Scale (BES)[28] is a 16-item questionnaire which assesses the presence of binge eating behaviour indicative of an eating disorder. The score ranges from 0 to 46 (non-binging <17; moderate binging = 18-26; severe binging = 27 and higher), which in this research had an adequate internal consistency (a = 0.84).

Eating Disorder Inventory-2 (EDI-2)[29] aims at quantifying some psychological and behavioural features. It consists of 64

questions grouped into 11 scales. For each item, the participants are asked to answer by using the following frequency adverbs: "always", "usually", "often", "sometimes", "rarely", and "never". The rating is measured with a score between 0 and 3: the maximum score of 3 corresponds to the intensity of the symptom ("always" or "never" depending on whether the direction of the item is positive or negative), score 2 corresponds to a degree intensity immediately below ("usually" or "rarely"), score 1 to an even lower level of intensity ("often" or "sometimes"), while a score of 0 is assigned to the three "asymptomatic" answers. So, those items with a positive direction are assigned the following scores: always = 3, usually = 2, often = 1, sometimes = 0, rarely = 0, never = 0; items with a negative direction are evaluated in the opposite way: never = 3, rarely = 2, occasionally = 1, and often, usually, always = 0. The sub-scale scores are calculated by simply adding all the scores of items of each specific sub-scale.

This research availed the *Impulse Regulation Scale* with an adequate internal consistency (a = 0.82). This scale shows the ability to regulate impulsive behaviour, especially binge behaviour.

Three Factor Eating Questionnaire (TFEQ)[30] is a self-report questionnaire consisting of 51 items. The questionnaire refers to daily dietary practice and measures three different aspects of eating behaviour: (1) restrained eating (conscious restriction of food intake in order to control body weight or to promote weight loss – cut-off: ≤11; a = 0.79); (2) uncontrolled eating (tendency to eat more than usual due to a loss of control over intake accompanied by subjective feelings of hunger – cut-off: ≤8; a = 0.81): (3) emotional eating (inability to resist emotional cues – cut-off: ≤7; a = 0.83).

Minnesota Multiphasic Personality Inventory-2 (MMPI-2)[31] consisting of 567 items with dichotomy answers (true/false) is most commonly used by mental health professionals to assess and diagnose mental illness. The MMPI is based on ten clinical scales that are used to indicate different psychotic conditions. In this research the scoring of the three following scales were taken into consideration: (1) Psychopathic Deviate Scale (Pd) (50 items) which measures social deviation, lack of acceptance of authority and amorality. This scale can be thought of as a measure of disobedience. High scorers tend to be more rebellious, while low scorers are more likely to accept authority. An adequate internal consistency was obtained in this research (a = 0.83); (2) Depression Scale (D) (57 items). The highest scores may indicate depression, while moderate scores tend to reveal a general dissatisfaction with one's own life. A sound internal consistency was obtained through this research (a = 0.81); (3) Hypomania Scale (H), with 46 items, identifies such characteristics of hypomania as elevated mood, accelerated speech, locomotive activity, irritability, flight of ideas, and short periods of depression. In this research the internal consistency was a = 0.79.

Results

The Statistical Package for Social Science (SPSS 10.1) was implemented to verify the hypothesis. The limited number of subjects enabled analysis of data through non-parametric statistics. In order to verify statistical differences between simple comparisons on paired data the Mann-Whitney (U) test[32] was applied. In order to verify statistical differences within phases (pre- Vs post-training), Wilcoxon Signed Ranks Tests[33] were calculated separately on paired data.

Table 1 synthesizes the means and standard deviations of *eating behaviour* and of *impulse regulation* obtained by the three groups: CBT alone; psychotherapy with Paroxetine (CBT+P); and psychotherapy with Venlafaxine (CBT+V) in pre- and post-treatments.

By comparing the total scoring in *BES* during the pre-treatments phase, no statistical differences between groups were noticed. Subjects who only underwent CBT had the same result than those who had addition of Paroxetine (CBT+P) [U = 64; Z = 0.35; p = 0.75] and Venlafaxine (CBT+V) [U = 59; Z = 0.62; p = 0.55]. There were no initial statistical differences between the two groups that received pharmacotherapy [U = 50; Z = 0.1; p = 0.99].

In the post-treatment phases, the presence of binge eating behaviour appeared to be the same in all groups. Subjects belonging to the CBT group obtained the same results as those belonging to the CBT+P [U = 58; Z = 0.68; p = 0.5] and the CBT+V groups [U = 47; Z = 1.36; p = 0.19]. No statistical differences between medication use were noticed [U = 41; Z = 0.69; p = 0.53].

All groups in post-treatment phases seem to equally benefit from the treatment. Comparing scores obtained by participants in the pre- and post-treatments, statistically significant differences were found in subjects undergoing CBT [Z=3.38, p < 0.001] and those with the addition of Paroxetine [Z = 2.848; p < 0.004] and Venlafaxine [Z = 2.859, p < 0.004].

For this research, *Impulse Regulation Scale* scores were taken into consideration. In the pre-treatment phase relative to each group, all groups showed the same difficulties to regulate impulsive behaviour. The CBT group showed the same impulse regulation as those belonging to the CBT+P [U = 68; Z = 0.12; p = 0.93] and CBT+V group [U = 64; Z = 0.33; p = 0.75]. No initial statistical differences between pharmacotherapy groups were found [U = 45; Z = 0.39; p = 0.74].

In post-treatment, no statistical differences between groups were observed. The CBT group achieved the same results as the CBT+P [U = 60; Z = 0.56; p = 0.58] and CBT+V group [U = 64; Z = 0.32; p = 0.75]. No statistical differences between the use of Paroxetine and Venlafaxine were found either [U = 39; Z = 0.84; p = 0.44].

Groups	Phases	*Binge Eating Disorder*				*Impulse Regulation Scale*			
		MIN	MAX	M	SD	MIN	MAX	M	SD
CBT (N=10)	Pre	28	35	31.43	2.41	74	94	85.93	6.84
	Post	25	33	28.71	2.46	71	91	83.07	6.67
CBT+P (N=10)	Pre	26	35	30.90	3.54	77	94	86.80	5.29
	Post	24	31	27.90	2.85	74	91	82.10	5.72
CBT+V (N=10)	Pre	27	35	30.80	2.78	83	94	87.80	3.91
	Post	24	31	27.20	2.57	79	90	83.80	3.71

Table 1 – Minimum and maximum scores, Means and Standard Deviations of eating behaviour and of impulse regulation obtained by three differential groups.

Groups	Scales	Pre-Treatment				Post-Treatment			
		MIN	MAX	M	SD	MIN	MAX	M	SD
CBT	restrained eating	5	9	6.64	1.28	5	8	5.86	.95
	uncontrolled eating	13	16	14.71	1.07	11	15	12.93	1.21
	emotional eating	8	13	9.93	1.21	7	11	8.57	1.22
CBT+P	restrained eating	5	9	6.50	1.43	5	7	6.00	.82
	uncontrolled eating	13	16	14.10	1.11	10	13	11.60	1.07
	emotional eating	8	13	10.70	1.64	8	11	9.80	1.03
CBT+V	restrained eating	5	8	6.10	1.11	4	7	5.50	.85
	uncontrolled eating	12	16	13.90	1.37	10	13	11.40	1.17
	emotional eating	9	13	10.60	1.43	7	11	9.10	1.19

Table 2 – Minimum and maximum scores, Means and Standard Deviations of different aspects of eating behavior (restrained eating, uncontrolled eating and emotional eating) obtained by three differential groups

Groups	Scale	Pre-Treatment				Post- Treatment			
		MIN	MAX	M	SD	MIN	MAX	M	SD
CBT	Psychopathic Deviate (Pd)	68	85	74.14	5.02	60	80	66	5.38
	Depression (D)	63	81	72.50	5.58	61	78	69.86	5.39
	Hypomania (H)	39	75	62	8.15	41	72	59.50	7.29
CBT+P	Psychopathic Deviate (Pd)	70	84	74.80	3.97	67	80	71.40	3.72
	Depression (D)	66	76	70.80	3.91	64	74	67.80	3.58
	Hypomania (H)	46	70	60.30	7.94	40	63	54.10	8.08
CBT+V	Psychopathic Deviate (Pd)	70	85	76.20	5.41	66	80	72.90	5.06
	Depression (D)	65	80	70.80	4.76	61	75	66.60	4.69
	Hypomania (H)	42	72	60.10	10.67	41	69	54	10.27

Table 3 – Minimum and maximum scores, Means and Standard Deviations of different aspects of Psychopathic Deviate obtained by three differential groups

All groups seemed to benefit from the treatments. In fact, comparing the scores obtained by participants in the pre- and post-treatments, statistically significant differences were observed in subjects who underwent CBT [$Z = 3.38$, $p < 0.001$] as well as in subjects supported by Paroxetine [$Z = 2.84$; $p < 0.005$] and Venlafaxine [$Z = 2.97$, $p < 0.003$].

Table 2 synthesizes the means and standard deviations of different features of eating behavior (restrained eating, uncontrolled eating and emotional eating)showed by the three groups (CBT, CBT+P, and CBT+V) in pre- and post-treatment.

In eating behaviour as well, all groups in pre-treatment phases appeared to be equivalent. The CBT group had the same mean result in restrained eating than those subjects who also underwent pharmacotherapy [CBT+P: $U = 65$; $Z = 0.33$; $p = 0.74$; and CBT+ V: $U = 53$; $Z = 1.03$; $p = 0.55$]. In the pre-

training no statistical differences between groups with pharmacotherapy were noticed [U = 42; Z = 0.59; p = 0.58].

By analyzing the groups in pre-treatment phases no statistical differences in uncontrolled eating behaviour and emotional eating behaviour were found. In pre-treatment phase, the CBT subjects had the same statistical mean in uncontrolled eating [U = 48; Z = 1.33; p = 0.21] and in emotional eating [U = 48; Z = 1.32; p = 0.21] as those who took Paroxetine. No statistical differences were found when comparing CBT subjects with those that were taking Venlafaxine [uncontrolled eating: U = 48; Z = 1.33; p = 0.21; emotional eating: U = 48; Z = 1.32; p = 0.21]. In the pre-training phase there were no statistical differences between groups with pharmacotherapy [uncontrolled eating: U = 46; Z = 1.44; p = 0.17; emotional eating: U = 51; Z = 1.12; p = 0.28] were found.

All groups showed indistinctively less difficulty on restrained eating habits. In fact, by comparing post-training scores, the participants of CBT obtained the same results as those treated with Paroxetine [U = 61; Z = 0.56; p = 0.62] and Venlafaxine [U = 58; Z = 0.75; p = 0.51]. Therefore CBT alone appeared to be less effective on reducing uncontrolled eating than those with the addition of Paroxetine [U = 30; Z = 2.4; p < 0.02] and Venlafaxine [U = 26; Z = 2.6; p < 0.009]. Participants who underwent only CBT presented with less difficulties on emotional eating control than those with Paroxetine [U = 31; Z = 2.31; p < 0.02], but they achieved the same post-treatment score as those supported by Venlafaxine [U = 52; Z = 1.08; p = 0.31].

Comparing post-treatment outcomes, the effectiveness of Paroxetine and Venlafaxine appeared to be the same on restrained eating behaviour [U = 34; Z = 1.2; p = 0.25], on a better controlled eating behaviour [U = 45; Z = 0.39; p = 0.69] and on a higher emotional eating control behavior [U = 33; Z = 1.29; p = 0.2].

Comparing pre- and post-treatment results helped to observe a significant improvement in all groups. Participants who followed only CBT showed less difficulty to restrained eating behaviour [Z = 2.6; p < 0.009] in post-treatment. The same results were observed in those supported by Venlafaxine [Z = 2.12; p < 0.03], while no statistical differences were detected in a post-treatment phase in those groups supported by Paroxetine [Z = 1.89; p = 0.06].

Moreover it was possible to observe a considerable decrease in uncontrolled eating behaviour in all groups [CBT: Z = 3.49; p < 0.0001; CBT+P: Z = 2.84; p < 0.005; CBT+V: Z = 2.88; p < 0.004]. The same results were observed in the way emotional eating was handled. All groups benefited from treatments [CBT: Z = 3.27; p < 0.001; CBT+P: Z = 2.46; p < 0.01; CBT+V: Z = 2.87; p < 0.004].

Table 3 synthesizes means and standard deviations of Psychopathic Deviate (Pd), Depression (D) and Hypomania scales (H) obtained by the three groups (CBT, CBT+P, and CBT+V) in pre- and post-treatments.

As evidence of the homogeneity of the groups, the comparisons revealed no statistically significant differences in the pre-treatment phase. The CBT group subjects and those who received Paroxetine [Pd: U = 58; Z = 0.67; p = 0.51; D: U = 55; Z = 0.85; p = 0.39; H: U = 63; Z = 0.41; p = 0.71] showed similar scores. Likewise, the CBT group subjects and those treated with Venlafaxine [Pd: U = 53; Z = 0.99; p = 0.34; D: U = 58; Z = 0.71; p = 0.51; H: U = 65; Z = 0.26; p = 0.79] showed similar scores. The two groups treated subsequently with pharmacological support showed similar initial scores as well [Pd: U = 44; Z = 0.46; p = 0.68; D: U = 50; Z = 0.1; p = 0.99; H: U = 44; Z = 0.45; p = 0.68].

Comparing the results obtained in the post-treatment phase instead, those participants exposed to CBT alone showed a greater reduction of Pd compared to those who had taken Paroxetine [U = 23; Z = 2.76; p < 0.005] and Venlafaxine [U = 23; Z = 2.77; p < 0.005], whereas no differences were found comparing the scores obtained post-treatment in both groups of subjects with pharmacological treatments [U = 41; Z = 0.65; p = 0.53].

In post-treatment, the CBT group participants showed similar scores when compared to those taking Paroxetine [D: U = 54; Z = 0.91; p= 0.37; H: U = 41; Z = 1.67; p = 0.09] and Venlafaxine [D: U = 44; Z = 1.49; p = 0.14; H: U = 49; Z = 1.2; p = 0.23]. There have been no further significant differences in scores obtained post-treatment by the two pharmacotherapy groups [D: U = 39; Z= 0.84; p = 0.44; H: U = 0.47; Z = 0.23; p = 0.85].

All participants seem to have benefited from the proposed treatment. The CBT group had a significant reduction of Pd [Z = 3.3; p < 0.001], D [Z = 3.37; p < 0.001] and H [Z = 3.19; p < 0.001].

A similar result was found by comparing the pre- and post-treatment scores of the subjects supported by Paroxetine [Pd: Z = 2.7; p < 0.007; D: Z = 2.82; p < 0.005; H: Z = 2.82; p < 0.005].

Even in the group treated with Venlafaxine, a significant reduction of Pd [Z=2.87; p< 0.004], D [Z = 2.84; p < 0.004] and H [Z = 2.81; p < 0.005] was confirmed.

Discussion

The use of pharmacological therapy for overweight patients with BED has been less thoroughly studied. SSRIs (Citalopram, Sertraline, Fluoxetine, and Fluvoxamine) have mainly been used as the active compound in the pharmacological trials of patients with BED in order to improve mood symptoms and weight

loss.[34] Likewise, in many cases, promising results have been obtained with Venlafaxine in BED.[35]

Most of the research has focused on specific aspects of binge eating disorder, such as reduction in binge frequency and weight reduction. In general the results are associated with higher discontinuation rates.[36]

In this research, we did not only focus on the binge eating behaviour and impulse regulation in patients with BED. The main objective of this research was to analyze some aspects of eating behaviour (restrained eating, uncontrolled eating and emotional eating) and, more specifically, different psychotic conditions (psychopathic deviate, depression and hypomania).

The first hypothesis of this research was to verify differences between patients with binge eating disorder that followed CBT either with or without a pharmacotherapy support. The results confirmed that CBT and pharmacotherapy are equally effective in the treatment of BED and equally modified patients' impulse regulation. Paroxetine and Venlafaxine medications did not enhance the control of binge eating or guarantee management of impulse regulation better than CBT alone.

This research also aimed at evaluating the efficacy of CBT with or without pharmacotherapy on some factors related to eating behaviour, such as the tendency to consciously monitor and reduce the caloric intake (restriction), the tendency to lose control on food intake (uncontrolled eating) and the conscious perception of the sensation of craving for food (emotional eating). The results suggest that CBT offers the same results regarding the reduction of caloric intake (restriction) as pharmacological treatment. It is less efficient in reducing the lack of control in food intake (uncontrolled eating), although it helps to reduce the sensation of craving for food (emotional eating) compared to pharmacotherapy.

In this research the effects of standardized treatments of CBT with or without the use of pharmacotherapy with bio-equivalent doses of Paroxetine and Venlafaxine were analyzed on psychopathic deviation, depression, and hypomania. The results confirmed that CBT showed a greater reduction of psychopathic deviation compared to those groups who underwent pharmacotherapy. Moreover, pharmacotherapy led to a higher reduction of depression and hypomania than CBT alone.

The second hypothesis was to verify if the SSRI Paroxetine and SNRI Venlafaxine were equally effective on impulse regulation, eating behaviour and personality features. The analysis showed that Paroxetine and Venlafaxine were equally effective on binge eating control and impulse regulation, but some differences in reducing dysfunctional eating behavior were found. Venlafaxine, compared to Paroxetine, seems to offer a greater improvement in emotional eating and restriction eating behavior. In fact CBT could be efficient to assess the tendency to reduce caloric intake (restriction) and to reduce the sensation of craving for food (emotional eating) more than Paroxetine alone. In order to reduce the tendency to lose control on food intake (uncontrolled eating) it could be helpful to administer Paroxetine or Venlafaxine.

Limitations

While the clinical groups were equivalent in all the parameters taken into consideration in the pre-treatment phase, the absence of a control group (no treatment) significantly reduced the possibility to accurately verify the conclusion. Due to ethical reasons we were not allowed to select a group of patients without any specific treatment. In order to correct this weakness in the research, it might be helpful to extend the sample and analyze the changes over a longer period of time.

It is relevant to analyze appropriately these aspects through controlled trials in order to test the efficacy and long-term outcome of psychotherapy, pharmacotherapy, and psychotherapy in combination with pharmacotherapy for treating BED.

Conclusion

In conclusion, patients with eating disorders usually suffer from other psychiatric disorders besides their eating disorder. Many results also confirm substantial comorbidity among obesity, BED, mood and anxiety disorders and metabolic syndrome in weight loss seeking populations.[37]

In such cases, it is important to understand the characteristics of the additional psychiatric disorders and the impact these ones have throughout the treatment.

As underlined by American Dietetic Association (ADA) Reports,[38] understanding the complexities of eating disorders, such as influencing factors, comorbid illness, medical and psychological complications, is critical in the effectiveness of the treatment of eating disorders.

Eating disorders are complex medical illnesses since they have psychological, behavioural, and physiological components. Previous researchers underlined the importance to investigate gender differences in binge eating and associated behavioural correlates[39] and, in order to prevent eating disorders, it is important to carry out individual treatment even on personality traits if the individual disorders have already occurred.[40] Of course, a multidisciplinary approach involving a collaborative team of psychological, nutritional, and medical specialists as underlined in this research must be pursued in order to obtain important and at least short-term results.[41]

The results of this research confirm the need to analyze BED from an integrative perspective and to suggest treatments based on an interdisciplinary approach. The psychological (CBT) and pharmacological (Venlafaxine and Paroxetine) therapies were

both efficient in different ways on the reduction of all the negative variables related to eating disorder. However any treatment could be inadequate in the absence of an accurate diagnosis that takes into consideration biological, genetic, psychological and nutritional components.

The assessment phase still plays an important role in determining which treatment is best for each patient. Accuracy in the medical examination when dealing with medical issues, as well as during the assessment examination and the psychological functioning evaluation is recommended.

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Review Article

Cognitive Behavioural Therapy for anxiety in children and adolescents with Autism Spectrum Disorder

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Abstract
This article is a review of the use of Cognitive Behavioural Therapy for anxiety in children and adolescents with high functioning Autism Spectrum Disorders (ASD). It first briefly outlines some of the key features of ASD, comorbid anxiety, and the increasing necessity to identify effective intervention strategies for use in this group of individuals, before providing a critique of the literature available. It looks at the adaptations that are commonly suggested to tailor a CBT intervention to the specific needs of an ASD population, and at the studies done so far.
Autistic Spectrum Disorder is a term used to describe a condition in which the person has difficulties in social reciprocation, communication and ritualised or rigid behaviour. Most people on the Autistic Spectrum will have social skills difficulties but not necessarily meet criteria for other clinical problems. Look for associated co-morbid conditions such as Depression and Attention Deficit Disorder. A common associated presentation which can be debilitating but often overlooked is anxiety.
People on the Autistic Spectrum should have access to a range of treatments for anxiety as other clinical populations. Modified Cognitive Behavioural Therapy can be successfully used to manage anxiety disorders in people on the Autistic Spectrum.
Keywords: ASD, Anxiety, CBT, Group therapy, Autism, children, Adolescent
Abbreviations: ASD;Autism Spectrum Disorder. CBT;Cognitive Behavioural Therapy.

Description of the disorder

Autism Spectrum Disorders (ASD) is the umbrella term increasingly used to describe the set of pervasive developmental disorders that included the diagnosis of Autism, Asperger's Syndrome, and Pervasive Developmental Disorder Not Otherwise Specified under DSM IV. These are a group of disorders characterised by pervasive difficulties in a combination of the key areas of social communication interaction, and restrictive repetitive behaviours or activities [1, 2]. The *Diagnostic and Statistical Manual of Mental Disorders (*the *DSM-5),* released by the American Psychiatric Association, officially eliminated many familiar autism spectrum diagnoses and now incorporated them into the single diagnosis of autism spectrum disorder. In DSM-IV, Asperger Syndrome was diagnostically differentiated from Autism by the lack of a significant language delay and intellectual functioning within the normal range.

The epidemiology of ASD is approximately estimated 30 in 10,000, although with increasing awareness of the disorder, this has led to greater rates of diagnosis, more recent estimates suggest the rate may be as high as 60 in 10,000 [3]. ASD may be as common as 1 in every 68 children according to the United States Centre for Disease Control [4].

Difficulties with an understanding of prevalence possibly related to early studies relying on clinically identified cases rather than community-based surveys, which may have resulted in cases not in treatment were being missed, and possibly only the most severe cases being recorded. Previous estimates may also have been incorrect due to previous narrower case definitions. As sampling methods have improved and better diagnostic instruments are used more cases have been identified and there has been a better delineation of ASD from other psychotic disorders. As more children with ASD are identified, there will be a likely rise in the number of families and children seeking treatment.

Comorbidities

There are very high levels of co-morbid psychiatric difficulties amongst this population with estimates ranging from 7-15%. Anxiety related concerns are among the most common presenting problems for school age children and adolescents with ASD [5]. Several studies have examined the prevalence of anxiety within the ASD population. A review by white et al [6] of 11 such studies reported a prevalence to range from 11-84%. This large range in the prevalence may be accounted for by difference in methods used to measure anxiety, differences in definitions and in diagnostic subtypes.

Studies have also looked at prevalence rates of anxiety within the ASD population to other populations. Compared to groups of typically developing children, those with autism had a higher occurrence of anxiety [7, 8]. Comparison with other groups considered to be at risk (children with conduct disorders and learning disabilities) children with ASD were more likely to be diagnosed with an anxiety disorder and/or have more intense anxiety symptoms [9,10].

A formal diagnosis of anxiety disorder in this group is hard for therapists due to overlap between comorbid anxiety and the core symptoms of ASD makes. Several anxiety disorders in DSM- IV and ICD 10 have autism as an exclusion criterion, implying that an anxious procession style is a feature of ASD.

The development of anxiety among children with ASD may relate to their cognitive impairment as they may lack the cognitive flexibility to generate strategies to adapt to varying circumstances and may experience distress over even trivial changes in the environment. The information processing style in children with ASD termed 'weak central coherence' is similar to non ASD anxious children whereby they selectively attend to threatening cues which results in the misinterpretation of ambiguous situations as threatening [11,12]. As a consequence these cognitive deficits can result in a repertoire of social and communication difficulties resulting in children experiencing severe difficulties in social relationships which may in turn lead to the development of anxiety [13]. If a child or adolescent has a co-occurring anxiety disorder, this could further negatively impact on the overall social impairment associated with ASD. This can impact on the child or adolescents ability to participate in activities at school, at home and within the community. Children with significant anxiety symptoms are at risk for serious educational difficulties, later unemployment, substance abuse and other psychiatric problems [14].

Some of the most frequently reported anxiety disorders and symptoms seen in children with Autistic Spectrum disorders are simple phobia, generalised anxiety disorder, separation anxiety disorder, obsessive-compulsive disorder and social phobia.

Treatment with Cognitive Behavioural Therapy

Pharmacological and psychosocial treatment have been the most common approaches to the treatment of anxiety in children with ASD but no single anxiety treatment has emerged to attain well established or probably efficacious empirically supported treatment status for children with an autistic spectrum disorder. Evidence for pharmacological intervention is limited. Also the effects of medication only appear to last as long as the medication is used, with relapse once regime is ceased.

The recommended treatment of choice by NICE guidelines for mood and anxiety disorders is cognitive behavioural therapy (CBT) and the primary psychosocial treatments have used CBT.

Despite the fact that CBT has been shown to be an effective empirically supported treatment for typical children, there continues to be differing views as to whether or not it can be used effectively with other populations. Some of the difficulties associated with treating children with ASD are due to suggestions from research that children with ASD have difficulty in identifying emotions and cognitions both in themselves and others. As CBT relies on the child's ability to infer their own emotional states and thoughts in order to shift their cognitive style and in turn their anxious behaviour, standard CBT treatments need modification to address the difficulties associated with this.

Although there is recognition of the high comorbidity of anxiety with ASD, there have also been suggestions to the use of strict behavioural analysis [15] and an argument against using a cognitive component to treat this population. Lindsay [16]provides a different view, arguing children with ASD can benefit from the use of a cognitive component.

Various modifications have been proposed on the approach of CBT in this population. Some of the models have suggested adjustment of the developmental level to reflect the child's ability, the use of coping model instead of curative model, the involvement of caretakers, and extending treatment both by the number of sessions and by overall session duration [17]. Attwood [18] has recommended the use of role-plays and visuals, the involvement of special interests of the young person, the adjustment of material according to the developmental level and the incorporation of a social skills module due to the vast deficits associated with ASD. Anderson and Morris [19] recommend a more directive approach to treatment and the use of specifically in vivo practice to aid in the generalisation of skills. Each of these variations may contribute differently to the adaptation of CBT to meet the specific needs of the child being treated; however, the most appropriate pattern of practical and functional strategies is yet to be determined.

Chorpita and Daleiden [20] in their review of evidence based treatment for children and adolescents noted the most commonly used techniques to treat anxiety in typically developing children. These include exposure, relaxation, cognitive restructuring and modelling in that order. The most commonly used techniques to treat ASD include communication skills training, modelling, social skills training, goal setting and parent psycho-education.

CBT generally consists of six components which include assessment of the nature and degree of the disorder, affective education, cognitive restructuring, stress management, self-reflection and a schedule of activities to practice new cognitive skills. It is important to ensure that the young person has the same definition and interpretation of words, and affective education can help increase their vocabulary of emotional expression.

Attwood [21] has described several intervention components which can be added to CBT. Some of the suggestions include; a) Increasing the use of visual aids. b) Associating emotions with tangible objects. c) An emphasis on coping strategies that do not require the use of abstract language for instance the use of relaxation. d) Use of alternative communication modes. e) Embedding the use of preservative interests into CBT sessions. f) Increasing the focus on teaching social skills.

Attwood also developed the concept of an emotional toolbox and focused on working with the young person in identifying different tools to 'fix' problems that occur as a consequence of negative emotions including anger, anxiety and sadness. The 'tools' are further divided into those that constructively release or reduce energy and those that improve thinking. The therapist generally works together with the young person to draw a variety of tools and activities which encourage constructive emotions repair.

Cognitive restructuring aims to enable the young person to correct distorted conceptualisations and dysfunctional beliefs. It involves challenging the current thinking with logical evidence and ensuring rationalisation and cognitive control of their emotions. Young people with ASD can make false assumptions of their circumstances and intentions of others due to impaired or delayed theory of mind abilities. These young people also tend to make literal interpretations and are less able to seek alternative explanations or responses.

Summary of Case Reports, Case Series, and Randomised Control Trials

Method

Studies that used CBT with the aim of reducing anxiety symptoms in young people with an ASD diagnosis were looked at.

Search Procedures

A search was carried out in electronic bases: Psychinfo and Medline. The publication year was not restricted but the search was limited to English- language peer reviewed journals. Over the databases, the terms 'Asperger', 'Autism', or 'developmental disability', plus 'anxiety' or 'CBT' and the search was limited to children and adolescents.

Review of Case series and reports

There have been five case studies that used CBT in treatment of anxiety as well as one case report that used CBT in treatment of OCD in children with ASD.

The first case study by Reaven and Hepburn (2003)[22] reported a 7 year old girl with Asperger syndrome who markedly responded to a 6 month modified CBT treatment which was primarily tailored for her OCD. Afterwards, Greig and MacKay (2005) [23], Sze and Wood (2007) [24] and (2008) [25], Reaven et al (2009) [26], and White et al (2009) [27] reported further successful outcomes of using modified CBT for treatment of Anxiety in children with ASD. See table 1 for a summary of published case reports and series of studies.

Review of Randomised Control Trials

There have been eight studies that have met criteria for a randomised controlled trial that identified CBT as a treatment for anxiety in children with ASD. See table 2 for published randomised controlled trials.

Sofronoff, Atwood, and Hinton (2005) [28] evaluated the impact of a six week cognitive-behavioural intervention for anxiety in 71 school children aged between 10 to 12 with Asperger's Syndrome. The authors also looked at the potential impact of parent involvement on outcome. The diagnosis of Asperger's Syndrome was confirmed by semi-structured telephone interview and anxiety symptoms were based on parent report in the initial telephone interview. Children were randomly assigned to one of three groups: child based intervention, combined child and parent intervention or a waiting list group. The intervention focused on teaching the children strategies to manage feelings and expanding emotional knowledge and was delivered weekly in a group format. The focus was on teaching the children strategies to effectively manage feelings and expanding emotional knowledge. Parents served as co-therapists in the combined parent-child intervention as they were trained in all aspects of the intervention.

Using the Spence Child Anxiety Scale-Parent report, children in the combined parent-child intervention reported fewer symptoms of anxiety post–treatment and at a six week follow up than children in the child-only intervention. A child report measure (James and the Maths Test) was used to identify the number of strategies the child could identify for coping with anxiety. Compared to children on the waiting list, children who received either intervention were able to develop more coping strategies. Those in the combined intervention generated significantly more coping strategies at endpoint compared to those in the child only intervention.

Parental involvement is an important aspect of treatment of young people with ASD in ensuring better generalisation and therapy outcome. Authors of this study found that children whose parents were involved in treatment were significantly more improved at follow up than those whose parents were not involved. There are different models of parents involvement and include either only direct participation in each session or

Table 1: A Summary of Published Case Reports and Series of studies using CBT for anxiety symptoms in young people with an ASD diagnosis

Author (year)	Sample	Anxiety Measure	Characteristics of intervention	Outcome
Reaven & Hepburn (2003)[22]	a 7 year old girl with Asperger syndrome		6 months modified CBT treatment based upon the work of March and Mulle	Obsessive-compulsive symptoms improved markedly
Greig and MacKay (2005) [23]	12 year old male with ASD and unspecified anxiety disorder	TSCC, Teacher Report, SWQ	15 sessions	Anxiety score on TSCC reduced from 19 to 5. Teacher report suggested improvements at school.
Sze and Wood (2007) [24]	11year old female SAD, OCD, GAD, HFA	ADIS	16 sessions 90 minutes each over 4 months family cognitive behavioural therapy (FCBT)	No longer met criteria for SAD, GAD or OCD on the ADIS by child or parent report
Sze and Wood (2008) [25]	10 year old male with ASD,GAD, SAD	ADIS, CGI, MASC, CBCL, SSRS, VABS	Enhancing CBT	No longer met criteria for Social phobia or GAD, on the ADIS, improvement CGI , MASC
Reaven et al (2009) [26]	7 male, 3 female mean age 11years, 12 weeks Active Treatment 10 parent-child dyads(n = 10) Wait List Control (n = 23)based on order of enrolment, not random assignment	SCARED	12 weekly sessions of 1.5 hours Large group time, separate parent and child group meetings, and parent-child dyads	Parent report on SCARED showed significant decrease in severity of anxiety symptoms in treatment group
White et al (2009) [27]	14 year old male with ASD, 14 yr old female with PDD-NOS,12 year old male with ASD, 12 year old female with ASD	ADIS	MCIT 12-13 individual therapy modules delivered over 11 weeks.	On the CASI-20 parent rated measure of anxiety, 3 out of 4 participants demonstrated significant improvement from baseline to endpoint.

CY-BOCS children's Yale-Brown Obsessive Compulsive Scare, **SAD**- Separation Anxiety Disorder, **OCD**- Obsessive Compulsive Disorder, **GAD**-Generalised Anxiety Disorder, **HFA** – High Functioning Autism, **ADIS** – Anxiety Disorder Interview Schedule, **CGI** – Clinical Global Scale, **MASC** – Multidimensional Anxiety Scale for Children, **CBCL** – Child Behavioural Checklist, **SSRS** –Social Skills Rating System, **VABS** – Vineland Adaptive Behaviour Scales, **SWQ** – Social Questionnaire, **MCIT** – Multi- Component Integrated Treatment, **PARS** – Paediatric Anxiety Rating Scale, **RCMSA**-Revised Children's Manifest Anxiety Scale, **SRS**- Social Responsiveness Scale, **CASI-Anx** - Child and Adolescent Symptom Inventory-4 ASD Anxiety Scale

Table 2: Published randomised controlled trials of CBT

Author (year)	Age range/ Sample size	Anxiety Measure	Characteristics of intervention	Characteristics of Controlled	Outcome
Sofronoff, Atwood, Hinton (2005) [28]	age 10-12 (n=71)	SCAS, SCAS-Parent, child report measure	a 6 week CBT child based (n=23) or combined child and parent (n=25) intervention	a waiting list group	Significant decreases Parent reports SWQ at follow-up and a significant increase in the child's ability to generate positive strategies in an anxiety-provoking situation.
Chalfant, Rapee, and Carroll (2006) [29]	age 8-13 (n=47)	ADIS, SCAS, Revised Children's Manifest Anxiety Scale, Children's Automatic Thoughts Scale, SDQ-Parent, SCAS-Parent	a 12 week group CBT based on 'Cool Kids' program(n=28)	Approx. 7 months waiting list (n=19)	71.4% of the treated children no longer met criteria for an anxiety disorder compared to 0% in the wait list condition (n=19)
Wood et al (2009) [30]	ages 7-11 (n=40)	Anxiety symptom checklists at baseline and post treatment/ post waitlist	16 sessions of standard CBT augmented with multiple treatment components (n=17)	A 3 month wait list (n=23)	78.5% CGI improved compared to only 8.7% of the waitlist group, Remission of anxiety in CBT group, but child reported anxiety had no significant effect
Sung et al (2011) [31]	age 9–16	SCAS-C,CGI-S	a 16-week CBT program	a Social Recreational (SR) program on anxiety	Children in both programs showed significantly lower levels of generalized

	(n=70)		(n = 36)	(n =34)	anxiety and total anxiety symptoms at 6-month follow-up on SCAS-C
Reaven et al (2012) [32]	age 7-14 (n=50)	ADIS-P	modified CBT (n=24)	TAU (n=26)	50% in the CBT compared to 8.7% TAU group had a clinically meaningful positive treatment response, group CBT intervention specifically developed for children with ASD may be effective in decreasing anxiety
White et al (2012)[33]	age 12-17 (n=30)	ADIS-C/P,SRS, CASI-Anx CGI-I, PARS	Multimodal Anxiety &Social Skills Intervention (MASSI) (n=15, 13 completed)	wait-list control (n=15, 12 completed)	16 % improvement in ASD social impairment MASSI is a feasible treatment program and further evaluation is warranted On the CGI-I, 6 of 15 (40 %) MASSI participants were rated as responders compared to 3 of 15 (20 %) of WL participants
Storch et al (2013)[34]	age 7-11 (n=45)	ADIS IV C/P, PARS,CGI, MASC-P, RCMAS	BIACA –CBT; child & parent focused sessions (n=22)	TAU(n=21)	18 (75 %) of CBT arm, were treatment responders, versus only 3 of 21 (14%) in the TAU arm. CBT adapted for anxious youth with high-functioning ASD demonstrates large effects in reducing anxiety symptoms.
McNally et al (2013) [35]	age 8-14 (n=22)	ADIS-P, SCAS-P, SCAS	a modified version of the Coping Cat program CBT package(n=12)	waiting-list (n=10)	ADIS-P 58% of children with CBT had no anxiety / 36% after 2 month follow up. A modified version of the Coping Cat program may be a feasible and effective program for reducing clinically significant levels of anxiety in children with ASD.

with a separate parent only component or both. It seems that regardless of which approach is used parent involvement increases the sustainability and success rate of CBT. Involvement of parents helps to improve their understanding of exposure and practice and helping the young person to learn how to master the skills on their own.

Limitations of this study include the reliance on the parent report of anxiety symptoms and both Asperger's Syndrome and anxiety symptoms were not formally diagnosed. Parents who were involved in the delivery of treatment may have had a more vested interest in their children's progress with higher expectations for improvement affecting outcome measure reports. However, no independent (blinded) ratings of anxiety were gathered.

Chalfant, Rapee, and Carroll (2006) [29] evaluated a 12 week group delivered cognitive –behavioural treatment for anxiety in 47 school children aged between 8 to 13 with ASD and no intellectual disability. The intervention was adapted from the 'Cool Kids' program (Lyneham et al, 2003), a 12 week group based activity for treatment of childhood anxiety. Cognitive strategies were simplified in the intervention, with a greater focus on visual aids, structured worksheets and homework and exposure and the programme was extended over a 6 month period of time.

The authors randomly assigned participants to either the CBT (n=28) or waiting list (n=19) before beginning of each treatment group. Those under waiting list condition were offered treatment after approximately 7 months, when the waiting list period ended. Multi-modal and Multi-person assessment of anxiety were used. At pre-treatment, over 75% of the sample met criteria for more than one anxiety disorder.

Structured diagnostic measures used in the study included the ADIS (Albano& Silverman, 1996), Spence Children's Anxiety Scale (Spence, 1998), The Revised Children's Manifest Anxiety Scale (Reynolds & Richmond, 1978), and Children's Automatic Thoughts Scale (Schniering& Rapee, 2002). Parent report measures included the SDQ-Parent Report (Goodman, 1997), and SCAS-Parent Report (Spence, 1998).

At post treatment, 71.4% of the treated children (n=28) no longer met criteria for an anxiety disorder compared to 0% in the wait list condition (n=19). It was also found that children in the CBT condition were largely able to identify their automatic thoughts indicating some theory of mind ability and had a significant reduction in automatic thoughts, in comparison to the wait list condition.

Limitations of this study include the small sample size so the data may not be reflective of the wider population with high functioning autism and anxiety. Also the lack of confirmation of the diagnosis of ASD by the investigating clinicians reduced

the validity of the participant's diagnostic status. Participants were accepted based on previous evaluations completed within the community setting.

There was no time spent with the waiting list group to help ensure that the benefits of treatment could be attributed to the treatment alone and not to time spent with the therapist. Also the issue of the waiting list group being aware of the treatment programme and knowledge of future treatment may have attenuated the response of those on the waiting list. Clinicians who implemented the CBT groups and collected the relevant pre-and post-treatment data were not blind to the study's aims.

Wood et al (2009) [30] used a standard CBT program augmented with multiple treatment components as a randomised controlled trial for 40 children aged between 7 to 11. It was designed to accommodate the social and adaptive skill deficit of children with ASD that could pose barriers to anxiety reduction. They also used a family based intervention program adapted for use with children with ASD. Enhancements included addressing of poor social skills, adaptive skill deficits, circumscribed interests and stereotypes, poor attention and motivation, common co-morbidities as well as school based problems. During modules, children were given social coaching by the therapist, parents and available school providers on appropriate ways to enter interactions and maintain conversation with peers.

Children were randomly assigned to 16 sessions of CBT (n=17) or a 3 month wait list (n=23). Independent evaluators blind to treatment condition, were involved in structured diagnostic interviews. Parents and children completed anxiety symptom checklists at baseline and post treatment/ post waitlist.

The Clinical Global Impressions Improvement Scale (CGI) criteria showed that 78.5% of the CBT group showed positive treatment response at post treatment as compared to only 8.7% of the waitlist group.

Children randomised to CBT had primary outcomes comparable to those of typically developing children receiving CBT for anxiety disorder, which were remission of all anxiety disorders for over half the children in immediate treatment at post treatment and follow up and a high rate of positive treatment response on the CGI. However child- reported anxiety did not yield a significant treatment effect.

Limitations of this study include the small sample size which precluded tests of moderation. The study was also undertaken by researchers who developed the intervention and would need independent replication to validate the intervention.

Also using measures not designed for children with ASD had major impact on the outcomes. The child report of Multidimensional Anxiety Scale for Children (MASC) scores did not yield a significant effect for treatment group largely due to a decrease in MASC scores from pre to post treatment for children in both groups. This may have been due to the MASC being not particularly effective in this population and children's scores at baseline were relatively low on average. Parental scores showed less of a change from pre to post treatment in the waiting list group. The MASC does not specifically measure OCD and GAD symptoms and as there was a wide range of anxiety symptoms, the type of change that some children may have experienced may not have been properly assessed.

Sung et al (2011) [31] compared the effects of a 16-week cognitive-behavioural therapy program and a Social Recreational (SR) program for 70 children with ASD aged between 9 to16. 36 of them were randomised to CBT and 34 to Social Recreational program. Children in both programs showed significantly lower levels of generalized anxiety and total anxiety symptoms at 6-month follow-up on SCAS-C. They suggest factors such as regular sessions in a structured setting, consistent therapists, social exposure and the use of autism-friendly strategies are important components of an effective framework in the management of anxiety in children and adolescents with ASD.

Reaven et al (2012) [32] used a modified CBT intervention for anxiety in 50 children aged between 7 to 14 with high-functioning ASD and anxiety, who were randomized to group CBT (n=24) or treatment-as-usual (TAU) (n=26) for 12 weeks. Independent clinical evaluators blind to condition, completed structured ADIS-P pre- and post-intervention condition. They found a significant difference between CBT and TAU group.

47 children completed either the CBT or TAU condition. They also had 3 and 6 month follow-ups. Results indicated markedly better outcomes for the CBT group. Clinician Severity Ratings, diagnostic status, and clinician ratings of global improvement showed significant differences by group. In the intent-to-treat sample, the CBT group, 10 of 20 children (50%) had a clinically meaningful positive treatment response, compared to 2 of 23 children (8.7%) in the TAU group. Initial results from this randomized, designed treatment study suggest that a group CBT intervention specifically developed for children with ASD may be effective in decreasing anxiety.

Limitations of this study include small sample size, lack of an attention control group, use of outcome measures normed with typically developing children, and no use of teacher or child measures. TAU remained variable, and the study did not

mention the situation of the children in TAU as were or weren't receiving any treatment.

White et al (2012) [33] combined treatment approaches, and evaluated the feasibility and preliminary outcomes of the Multimodal Anxiety and Social Skills Intervention (MASSI) program in 30 adolescents aged between 12 to 17 with ASD and anxiety symptoms of moderate to greater severity who were randomised to CBT (n=15) or Wait list group (n=15). A 16 % improvement in ASD related social impairment (within-group effect size = 1.18) was observed on a parent-reported scale. Although anxiety symptoms declined by 26 %, the change was not statistically significant. These findings suggest MASSI as a feasible treatment program and further evaluation is warranted. High subject adherence and therapist fidelity demonstrate the treatment was acceptable to families.

Storch et al (2013) [34] examined the efficacy of the Behavioural Interventions for Anxiety in Children with Autism (BIACA), a modular cognitive behavioural therapy protocol, relative to treatment as usual (TAU) among 45 children with ASD aged between 7 to 11. Children with clinically significant anxiety (including OCD), and no intellectual disability, were randomised to receive 16 sessions of weekly CBT (n=22, 2 drop out) or TAU (n=21). After screening, assessments were conducted at baseline, post-treatment, and 3-month follow up for only CBT group which was not blind. The raters were blind to treatment condition. They did also use both child- and parent-report versions of ADIS. Children receiving CBT showed substantial improvement relative to TAU on primary anxiety outcomes. Of 24 children randomised to the CBT group, 18 (75 %) were treatment responders, versus only 3 of 21 children (14%) in the TAU group. Treatment gains were generally maintained at 3-month follow up for CBT responders. They concluded that relative to usual care, CBT adapted for anxious youth with high-functioning ASD demonstrates large effects in reducing anxiety symptoms.

The limitations of this study include that only about 75% of the TAU children were in fact getting treatment of any kind at all, as 25% of their TAU weren't getting anything. Also TAU group was extremely variable, therefore the control group were getting a variety of treatments, or none, making comparisons with the children who received CBT difficult.

McNally et al (2013) [35] used a modified version of the Coping Cat Program in reducing anxiety in children with ASD. They randomly assigned 22 children with ASD aged between 8 to14, with clinically significant anxiety and no intellectual disability, to 16 sessions of the Coping Cat cognitive-behavioural therapy (CBT) program or a 16-week wait list group. They used ADIS-parent at pre-treatment and post-treatment phases, and they also video-recorded therapy sessions to check for treatment fidelity. Children in the CBT condition evidenced significantly larger reductions in anxiety than those in the waitlist. Treatment gains were largely maintained at two-month follow-up. Results provide preliminary evidence that a modified version of the Coping Cat program may be a feasible and effective program for reducing clinically significant levels of anxiety in children with high-functioning ASD.

The limitations of this study include small sample size which recommended statistical and effect size to be interpreted with caution, and also the outcome measures were largely based on parent- ADIS reports by parents who were not blind to the treatment. Also, examining treatment response was limited to the primary author who delivered all of the treatment. Similarly, with waiting list as a comparison, there was a danger of getting placebo effects with the intervention arm, especially with parent-report measures, as most parents were very keen to get any help at all for their children.

Discussion and future perspective

It is clear from the 8 randomised controlled studies that young people on the autistic spectrum benefit from some form of CBT when modified as part of a therapeutic package. Unfortunately it is not clear what specific aspect of the therapy is making the difference. Cognitive Behavioural Therapy has many components to it as well as the actual cognitive, i.e. 'thinking' part and behavioural part. Which bit of the therapy is making a difference to the anxiety? Is it the cognitive reframing, the relaxation, the exposure, the parental involvement, or simply the therapeutic relationship with a therapist? As with CBT studies which are delivered as part of a package, positive results are often obtained when there is no control group or when compared to a waiting list.

Other limitation to research papers cited above include fairly small sample sizes, and outcome measures that are normed with a non ASD cohort.

Only 2 studies had non waiting list comparison [32, 34]. These studies did show significant clinical improvement in anxiety levels. These studies have shown that CBT can be effective if modified for the ASD population. Many clinics often fail to pick up associated anxiety difficulties in the ASD cohort and if present, often are under the impression that CBT would not work in this population due to misunderstanding and ill-informed prejudices about the ASD population. As there is such a high comorbidity with anxiety disorders, young people on the autistic spectrum should be offered effective interventions such as CBT. Research should focus on modifications of the CBT

package to enable better engagement and better understanding of the CBT constructs.

Practice Points

- Children with high-functioning Autism Spectrum Disorder (ASD) are at high risk for developing significant anxiety
- Anxiety can adversely impact on functioning across school, home and community environments
- Cognitive Behavioural Therapy (CBT) is frequently used with success for children with anxiety symptoms
- Standard CBT treatments need modification to address the anxiety difficulties associated with ASD
- Modified CBT interventions for anxiety in children with ASD have also yielded promising results

Competing Interests
None declared
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Case Report

Cyclophosphamide and Doxorubicin-induced Acute Pancreatitis in a Patient with Breast Cancer

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Abstract
Predominantly occurring as a consequence of alcohol use or biliary stones, acute pancreatitis is rarely caused by chemotherapy. Lately, there have been increasing published reports and reviews of drug-induced pancreatitis from a wide array of antineoplastic drugs. We present a case of a patient recently diagnosed with Stage 3 breast cancer who was initially treated with cyclophosphamide and doxorubicin and subsequently developed acute pancreatitis, which recurred twice after a re-challenge with cyclophosphamide and epirubicin, a derivative of doxorubicin, given individually on two separate occasions. Acute pancreatitis reported in this case is defined by its clinical manifestations, biochemical evidence and imaging studies. To our knowledge, this is the first case of acute pancreatitis occurring in a patient with breast cancer associated with these chemotherapeutic agents.
Keywords: acute pancreatitis, chemotherapy, cyclophosphamide, doxorubicin, drug-induced pancreatitis
Abbreviations: CBC-complete blood count, FDA-Federal Drug Administration, NPO-nothing per os

INTRODUCTION

Although it is well appreciated that pancreatitis is frequently secondary to biliary tract disease and alcohol abuse, it can also be caused by drugs, trauma and viral infections, or even be associated with metabolic and connective tissue disorders.[1] Knowledge of the true incidence of drug-induced acute pancreatitis is dependent on the clinician's ability to exclude other possible causes, and by promptly reporting the occurrence. Based on individual case reports and case control studies of drug-induced acute pancreatitis, the estimated overall incidence ranges from between 0.1 and 2% of pancreatitis cases.[2,3] In particular, drug-induced acute pancreatitis is of mild severity and usually resolves without significant complications.[4]

Attempts have been made to categorize the risk of drugs causing acute pancreatitis. A previous classification system described by Mallory and Kern Jr. categorized drugs associated with acute pancreatitis as definite, probable, or possible.[5]Trivedi et al. proposed a newer classification system for commonly used medications associated with drug-induced pancreatitis. Class I drugs are those medications with at least 20 reported cases of acute pancreatitis and at least one case with a positive rechallenge. Drugs with fewer than 20 but more than 10 reported cases of acute pancreatitis, with or without a positive rechallenge, are designated into Class II. While those medications with 10 or less reported cases, or unpublished reports in pharmaceutical or FDA files, are grouped into Class III.[6]

Acute pancreatitis as a result of either doxorubicin or cyclophosphamide, or a combination of both, or fluorouracil or epirubicin is a rare occurrence and has seldom been reported in the literature. Even the drug package labels registered with the FDA do not indicate the possible occurrence of pancreatitis. In this case report, we present a rare occurrence of drug-induced acute pancreatitis after the completion of the first cycle of the chemotherapy protocol involving cyclophosphamide and doxorubicin in a patient with stage 3 breast cancer, with recurrences of acute pancreatitis after re-challenging with cyclophosphamide and a derivative of doxorubicin, given individually on two separate occasions.

CASE PRESENTATION

A 58 year-old female presented to the emergency room with a one day history of severe, diffuse, deep-seated abdominal pain that radiated to her back, associated with nausea and vomiting, and was unrelieved despite the intake of NSAIDs. There was no reported fever, chills, diarrhea, dysuria, or antecedent trauma. Her medical history is notable for well-controlled hypertension, hyperlipidemia and hypothyroidism for which she takes amlodipine, atorvastatin and levothyroxine. She was recently diagnosed with left-sided breast cancer, Stage III, two months prior to admission and underwent a left modified radical mastectomy. Three days prior to the hospital visit, she was given her first cycle of chemotherapy with Doxorubicin 60 mg/m^2 and Cyclophosphamide 600 mg/m^2 along with Pegfilgrastim 6 mg and Fosaprepitant 150 mg. She is a former cigarette smoker, drinks alcohol infrequently, and denies illicit drug use. Her family history is unremarkable.

Physical examination revealed stable vital signs without a fever (36.6°C). She had non-icteric sclerae and a dry oral mucosa. Chest exam revealed a well-healed left mastectomy scar and an infusaport located on the right anterior chest wall. Her breath sounds were clear bilaterally. Her heart sounds were normal. Her abdominal exam was significant for mild tenderness to palpation in the epigastric area without palpable masses, organomegaly or ascites. There was no evident ecchymosis

observed. The extremities were warm to touch with intact and symmetrical pulses, and without bipedal edema.

Initial work-up revealed an elevated leukocyte count of 42,000 with 80% neutrophils and 17% band forms. Basic metabolic panel was normal except for mild hyponatremia of 129 mEq/L. Serum amylase and lipase were markedly elevated at 2802 units/L and >2000 units/L, respectively. Liver function panel was normal (Alk phos 63 U/L [ref range 30-115 U/L], GGT 21 U/L [ref range 3-40 U/L], total bilirubin 0.90 mg/dL [ref range 0-1.5 mg/dL]). The coagulation profile was within normal range. Imaging of the abdomen with a CAT scan with intravenous and oral contrast showed haziness in the pancreatic fat plane suggestive of pancreatic inflammation, with no gallstones, focal abscesses, hepatic masses, or biliary ductal dilatation (Figure 1). Right upper quadrant ultrasound was essentially normal (Figure 2).

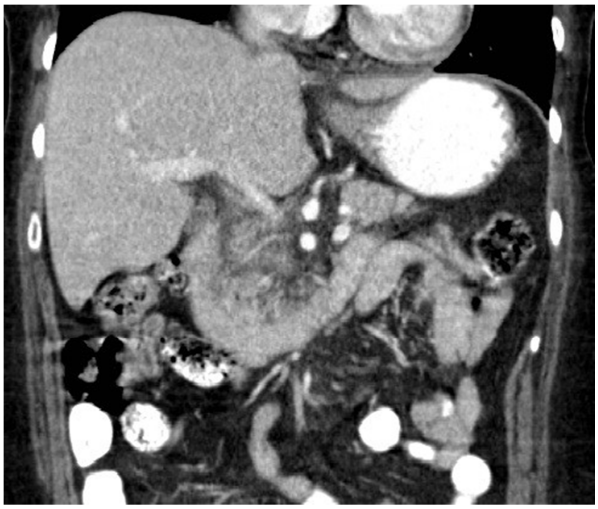

Figure 1. Coronal view of CT scan of abdomen and pelvis with IV and oral contrast showing haziness in the peripancreatic fat plane.

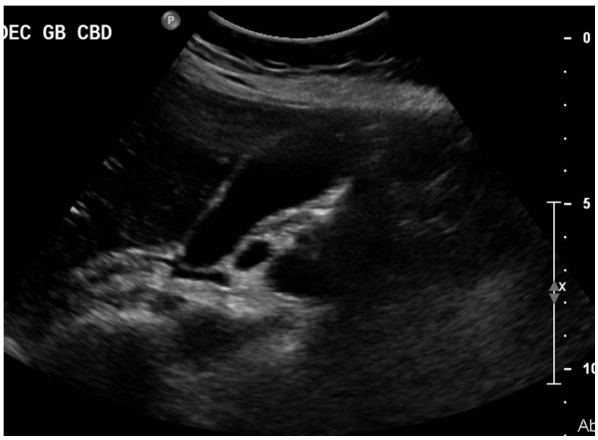

Figure 2. Sonogram of the right upper quadrant of the abdomen showing gallbladder devoid of gallstones and non-dilated common bile duct.

She was admitted to the medicine unit with the assessment of acute pancreatitis likely secondary to doxorubicin and cyclophosphamide. Intravenous fluid hydration with normal saline was initiated. She was kept NPO (*nothing per os*) and was started on empiric Imipenem and ~~IV~~ Esomeprazole. Her abdominal pain was controlled with intravenous morphine and her nausea with Ondansetron as needed. The serial basic chemistry panel was monitored and electrolyte deficits were replaced accordingly. Further work-up was performed to identify other possible etiologies of pancreatitis. The lipid panel was within normal limits (cholesterol 169 mg/dL [0-200 mg/dL], HDL 74 mg/dL, LDL 71 mg/dL and triglycerides 54 mg/dL [0-150 mg/dL]). The serum calcium levels remained within the normal range throughout her hospital stay. An abdominal sonogram demonstrated absence of gallstones or dilatation of the common bile duct, with a normal appearing liver parenchyma and pancreas. During her stay in the medicine unit, the patient's abdominal pain improved and she was gradually started on an oral diet, which she tolerated well. Her serum electrolytes remained stable, while her serial CBC revealed progressively decreasing trends in leukocytes, hemoglobin, hematocrit, and platelet count, findings which were attributed to her prior chemotherapy. Repeat serum amylase and lipase both trended downward. The patient was discharged with follow up in the Oncology clinic. A month later, she was started on another chemotherapy regimen that consisted of weekly administration of Paclitaxel 80 mg/m^2 which, over the next two months, the patient completed without any complications. Then, after explaining the risks of recurrent pancreatitis, the patient consented to have a trial of cyclophosphamide 500 mg/m^2 along with fluorouracil 500 mg/m^2. Five days after receiving the chemotherapy, the patient developed acute pancreatitis which was attributed to cyclophosphamide. She again made a full recovery at that time. Three weeks later, her chemotherapy regimen was again changed, to epirubicin 90 mg/m^2 and fluorouracil. Four days after receiving this regimen, she again, for the third time, had a recurrence of acute pancreatitis. At this time, a repeat abdominal sonogram revealed a 4mm echogenic focus adherent to the anterior gallbladder wall with a comet tail sign, suggestive of cholesterol crystals lodged within Rokitansky-Aschoff sinuses of the gallbladder wall. There were no visible gallstones. A subsequent MRI of the abdomen with contrast revealed a small rounded hypointensity in the dependent portion of the gallbladder wall that was suggestive of a gallstone, however, there was no biliary obstruction, choledocholithiasis or an obstructing pancreatic mass. At this point, chemotherapy was stopped and anastrozole along with radiation therapy was initiated. The patient continues to be followed regularly and has had no recurrence of pancreatitis since her last episode.

DISCUSSION

The case presented described the development of acute pancreatitis in a patient with breast cancer three days after receiving the chemotherapy regimen consisting of cyclophosphamide and doxorubicin. After re-challenging the patient with cyclophosphamide, and again a few weeks later

with a derivative of doxorubicin, epirubicin, acute pancreatitis recurred on each occasion. Despite the presence of cholelithiasis detected on the abdominal MRI, the temporal presentation of acute pancreatitis after chemotherapy exposure is highly suggestive of the role these chemotherapeutic agents played in triggering these three acute attacks. Acute pancreatitis was diagnosed based on the clinical suspicion and symptoms suggestive of ~~the~~ acute pancreatitis and was supported by the marked elevation in serum amylase and lipase, as well as, the radiologic evidence of pancreatic inflammation, both of which are markers of acute pancreatitis.

Chemotherapy-induced acute pancreatitis involving cyclophosphamide and doxorubicin either alone or in combination, is quite rare that even the drug labels registered with the FDA do not indicate acute pancreatitis as one of the possible complications. This scenario highlights the importance of drug surveillance and prompt reporting in order to maintain a credible drug safety database.

Though the drug latency, which is the interval between the initial exposure to the drug and the development of acute pancreatitis, differs variably, the present case is considered to have an intermediate latency (1-30 days). Other drugs may have short (< 24 hours) or long (>30 days) latency periods. Examples of drugs with short latency are acetaminophen, codeine, erythromycin and propofol. Intermediate latency drugs include L-asparaginase, pentamidine and stibugluconate. Drugs with long latency are estrogen, tamoxifen, valproate and dideoxyinosine.[7]

Based on the revised classification of Badalov et al, the combination of cyclophosphamide and doxorubicin is classified as Class IV drugs, which have the weakest association with acute pancreatitis due to limited information and the lack of adequate detailed case reports. Fluorouracil, which has been known to cause a gastrointestinal ulcer, is also categorized as a Class IV drug, while epirubicin, which is derived from doxorubicin, has not been classified, as it has not been reported before to cause acute pancreatitis. In implicating drugs in the etiology of acute pancreatitis, two conditions must be considered to weigh the strength of the association between the causality and the disease process, namely: a positive rechallenge test resulting in the recurrence of pancreatitis and a similar latency period between the drug exposure and development of the disease.[7]

The combination of drugs rather than a single agent was implicated for drug-induced pancreatitis in a previous case report that described the development of acute pancreatitis shortly after the second cycle of the chemotherapy regimen composed of cyclophosphamide, doxorubicin, and vincristine in a patient with mediastinal immunoblastic lymphoma. The pancreatitis episode resolved over 48 hours without complications.[8]

Another case was described in a patient with breast cancer developing acute pancreatitis four days after the third cycle of chemotherapy, which involved docetaxel and carboplatin.[9]

Toprak et al. reported the occurrence of acute pancreatitis in a patient with multiple myeloma after the initial treatment with the triple regimen chemotherapy protocol consisting of vincristine, doxorubicin, and dexamethasone. In this case report, symptoms suggestive of acute pancreatitis started to manifest on the first day of the treatment, with resolution following discontinuation of the drugs.[10]

Other antineoplastic agents for breast cancer associated with drug-induced pancreatitis are alemtuzumab, trastuzumab and tamoxifen. Extended use of these medications may cause chronic pancreatitis as a result of their causing repeated clinical or subclinical episodes of acute pancreatitis.[6] Most cases of drug-induced pancreatitis follow a mild clinical course.[7]

In a retrospective study involving 1613 patients diagnosed with acute pancreatitis in a gastroenterology center, the incidence of drug-induced pancreatitis had been reported in 1.4% of patients treated for acute pancreatitis. It has been observed that a higher incidence of drug-induced acute pancreatitis occurs in elderly or pediatric patients, and in those patients with inflammatory bowel disease or AIDS.[11]

The pathophysiology behind drug-induced pancreatic injury remains unclear. Potential mechanisms underlying such pancreatic injury might be related to drug hepatotoxicity which can be secondary to intrinsic toxicity of the drugs affecting the tissue, or due to an idiosyncratic reaction. In the vast majority of the cases, an idiosyncratic reaction could be the main pathway for tissue injury through a hypersensitivity reaction or production of toxic intermediate metabolites. Idiosyncratic reactions have a longer latency period of months to years before the onset of pancreatitis while the onset of hypersensitivity reactions is earlier (i.e. 1-6 weeks).[7]

CONCLUSION

Due to a variable latent period between the initial drug exposure and the onset of clinical symptoms, drug-induced pancreatitis must remain as a differential diagnosis in patients receiving chemotherapy regimens and presenting with the constellation of symptoms typical of acute pancreatitis. Due to the unclear pathogenesis of chemotherapy-induced pancreatitis, post-marketing surveillance and adverse drug reporting are paramount in elucidating the effect these drugs have on the pancreas.

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Case Report

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A case report of sertraline-induced hyperpigmentation

Fayyaz Khan and Carl Littlejohns

Abstract
This is a case report of a 27 years old Caucasian lady with Bipolar Affective Disorder that developed hyperpigmentation, after starting sertraline for low mood. Her current medications also included semi sodium valproate 1000 mg orally daily, quetiapine modified release 400 mg orally daily, tramadol 50mg orally twice a day and co-codomol orally on an as required basis for back pain. She denied any illicit drug intake and there is no significant past medical or family history. Sertraline was stopped and replaced by duloxetine, but unfortunately the hyperpigmentation persisted. Only one previous case of sertraline-induced hyperpigmentation was found.
Keywords: Sertraline, anti-depressant, SSRI, hyperpigmentation
Abbreviations: ICD- International Classification of Diseases

Introduction:

Sertraline is selective serotonin reuptake inhibitor (SSRI). It is a commonly prescribed antidepressant. The common side effects of SSRI's are nausea, vomiting, diarrhoea, dyspepsia, anorexia and weight loss.

To our knowledge this is the only second reported case of sertraline-induced hyperpigmentation. It is interesting to note that in some cases sertraline has been used as replacement medication following antidepressant induced hyperpigmentation. So it is important that both clinicians and patients are aware of this potential rare side effect of sertraline.

Case Report:

In this case report we present a 27 years old Caucasian lady that developed hyper pigmentation, after starting sertraline.

The patient, a 27 years old lady was diagnosed with Bipolar Affective Disorder (ICD-10)2 years ago. She was prescribed sertraline 50mg for low mood. Her current medications also include semi sodium valproate 1000 mg orally daily, quetiapine modified release 400 mg orally daily, tramadol 50mg orally twice a day and co-codomol orally on an as required basis for back pain. She was not prescribed any depot medications. To our knowledge she was compliant with her medication.

She responded well but reported that she had developed hyperpigmentation after four weeks. This persisted after suffering a recurrence of low mood and being seen in clinic 5 months later.

There is no significant past medical or family history. She has been on various psychotropic medications in the past including fluoxetine, venlafaxine, olanzapine and procyclidine.

Physical examination revealed focal hyperpigmentation limited to the upper lip. It was dark brown in color with sharply defined outline and was not associated with itching, redness, rash or excoriation. It was gradually getting darker in color and she had to wear a lot of make up to conceal it. The patient was referred to a consultant dermatologist for an opinion but unfortunately she did not attend her appointment. This has been acknowledged as a limitation of our case report. Routine blood tests were within the normal range. She also reported some weight gain with sertraline.

She did not report any previous history of dermatological disorders or any endocrine conditions and Addison's disease was excluded. She did not begin any new medication or vaccines prior to onset of the hyperpigmentation and denied ever having chlorpromazine, tricyclics, tetracyclines, amiodarone, hormone replacement therapy, aspirin, chemotherapy or minocycline. However three years ago, she had taken anti-malarial medication before going to the Dominican Republic. She also denied any intake of herbal medication, non-prescribed medication or illicit drugs.

She also denied excessive exposure to sunlight during the time of development of hyperpigmentation and she was not pregnant. There is no history of heavy metal exposure.

The probability of adverse drug reaction assessed by using Naranjo Scale indicated a probable association between the use of sertraline and hyperpigmentation. Subsequently her sertraline was stopped and replaced by duloxetine 30mg daily. Unfortunately the hyperpigmentation persisted after three off sertraline but is no longer worsening.

Discussion:

Bipolar Affective Disorder also known as bipolar disorder, manic-depressive disorder, or manic depression is characterised by two or more episodes in which patients mood and functionality is significantly disturbed, this disturbance on some occasions includes episodes of mania or hypomania with

elevated mood and increased energy levels and on others episodes of depression with low mood, tiredness and diminished pleasure in activities. Recovery is usually complete between these episodes. [1]

The pharmacological treatment of bipolar affective disorder depends on nature and degree of presenting episode and includes mood stabilisers like lithium, valproate, carbamazepine and lamotrigine, anti-psychotics like olanzapine, quetiapine, aripiprazole and risperidone and antidepressants like sertraline, citalopram and venlafaxine.

Sertraline, citalopram, escitalopram, fluoxetine, fluvoxamine and paroxetine selectively inhibits reuptake of serotonin, hence named selective serotonin reuptake inhibitor (SSRI).

In our case the patient was on semi sodium valproate and modified release quetiapine and was later prescribed sertraline to help with low mood.

A literature review of English language using PubMed database was done on 15th June 2013. The terms searched were "sertraline", "serotonin reuptake inhibitor", "SSRI", "anti-depressants", "hyperpigmentation", "pigmentation", and it found case reports of antidepressant associated hyperpigmentation with citalopram[2], mirtazapine[3] and imipramine.[4,5,6,7] It is interesting to note that in some of the case reports the antidepressants were replaced by sertraline after development of hyperpigmentation, but there was no record as to whether the lesion resolved.[2, 3,4]

Only one previous case of sertraline-induced hyperpigmentation was found[8], which also unfortunately persisted after discontinuation of the antidepressant.

As hyperpigmentation has also been reported with other SSRIs, clinicians should be more aware that hyperpigmentation might be related to the class effect, rather than the individual drugs.

Though the exact biological mechanism for the development of hyperpigmentation is not clear and further research is needed, the secretion of melanocyte stimulating hormone (a-MSH) is closely associated with skin pigmentation and serotonin and dopamine transmitters appear to be involved which may point to a possible mechanism for the hyperpigmentation.

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Case Series

Prevalence of Psychiatric Disorders Following Brain Injury

Nismen Lathif, Emily Phipps, Philip Alton and Devena Tyagi Sharma

Abstract

Brain injury is a major cause of mortality and morbidity all over the world and in Europe there is an estimated incidence of 235 brain injury inpatients per 100,000 population. Over the years, the medical care of brain injuries has developed with a resultant fall in mortality. However, with this fall in death rates the proportions of people with complications, especially the neuro-behavioural effects of brain injury, has risen. Of the complications, psychiatric disorders have a significant impact on the patient's quality of life and rehabilitation prognosis and so are an important consideration from both a care delivery and public health perspective. This paper analyses current literature, demonstrating a high prevalence of psychiatric disorders amongst this patient group. It also demonstrates the significant impact they have on patients, carers and families through an insightful case series.

Introduction

Brain injury is a major cause of mortality and morbidity all over the world and in Europe there is an estimated incidence of 235 brain injury inpatients per 100,000 population [1]. Over the years, the medical care of brain injuries has developed with a resultant fall in mortality. However, with this fall in death rates the proportions of people with complications, especially the neuro-behavioural effects of brain injury, has risen [2]. Of the complications, psychiatric disorders have a significant impact on the patient's quality of life and rehabilitation prognosis[3] and so are an important consideration from both a care delivery and public health perspective. This paper therefore aims to analyse the prevalence of psychiatric disorders following brain injury and highlight the practical and personal implications of these through an illustrative case series.

Depression Following Brain Injury

Jorge et al in 2004[4] conducted a prospective case controlled study on a sample of 91 patients with traumatic brain injury (TBI). Patients with penetrating head injury, spinal cord injury and severe deficits of comprehension was excluded and 27 patients without brain injury but with other trauma was included as controls. The sample was analysed at 3, 6 and 12 months with Present State Examination (PSE), structured clinical interview for DSM1V, and analysed with Mann Whitney and chi squared tests. The results showed that 33% of the TBI group had major depression compared to 22 % in the control group. Neuropsychological testing also demonstrated that depressed patients had a greater degree of impaired cognitive function. An earlier study with a larger sample was conducted by Kreutzer in 2001[5], studying 722 TBI patients (average time post injury for evaluation 2.5 years). Data was collected via survey, using the Neurobehavioral Functioning Inventory to identify depression; the response was studied by trained neuropsychologists and compared with DSM-IV Criterion for depression. A significant proportion (42%) of survey respondents met the DSM-IV criterion for depression. Fatigue, low concentration and frustration were most commonly reported symptoms. A similar study done by Seel et al in 2003[6], where 666 TBI outpatients from 17 centres was reviewed using DSM-IV Criterion, showed rates of major depression to be 27%.

Mania Following Brain Injury

Jorge in 1993[7] reviewed 66 patients with brain injury at 3, 6 and 12 month intervals to evaluate the prevalence of mania. The inclusion criteria was age above 18 years and absence of delirium, no previous history of mood disorder and absence of grave injuries to other areas of the body. Using the Present State Examination to gather data, 9% of the sample had symptoms in correlation with the DSM III criteria for mania.

Van Reekum in 1996[8] recruited 18 TBI patients attached to a rehabilitation unit for a study to evaluate mental illness in this population. 44% of patients had severe TBI while 56% had mild/moderate TBI; the average duration since TBI was 4.9 years. 27% met the DSM II criteria for bipolar affective disorder and 61% met criteria for depressive illness. The rate of anxiety disorder was 38% but psychosis was not reported.

Psychosis & Other Mental Illness Following Brain Injury

Fann et al in 2004[9] conducted a large prospective cohort study involving 1939 randomly selected TBI patients 1 year pre injury and 3 years post injury to study rates of psychiatric illness including psychosis. The sample was divided into the moderate/severe TBI and mild TBI compared to matched controls. The presence of psychiatric illness was detected by utilisation of mental health services by subjects, usage of psychotropic medication and presence of a psychiatric diagnosis in the records. Psychotic disorders were seen in 49% of the moderate to severe TBI patient group and for the mild TBI

group psychosis was seen in 34% of the sample. This is significantly greater than the rate seen in the control group. However the lack of definitive diagnostic criteria and confounding factors such as social circumstances and other physical health issues which may have strong associations with mental illness were not accounted for.

Another observational prospective study done by Rao et al in 2009[10] looked into prevalence rates of aggression in the 3 months following brain injury. Overt Aggression Scale was used by trained examiners in the assessment of aggression in a sample of 107 TBI patients. Comorbidities were analysed using General Medical Health Rating scale; psychosocial functioning was analysed by Social Functioning Exam and the Social Ties Checklist. Results showed the prevalence of aggression in the sample to be 28.4% and this subgroup was also associated with new-onset major depression. Only 63% of the already small sample completed the study and the drop out group was unaccounted for; this may negatively impact the results.

Keenan et al in 2008[11] studied prevalence of attention-deficit hyperactivity disorder(ADHD) in 2782 post TBI children and demonstrated chance of a diagnosis of ADHD two folds higher amongst children with a head injury before age 2. Jellinger in 2004[12] studied links between brain injury and dementia, and found that although cognitive deficit was associated with brain injury, there was no established link between development of dementia and brain injury. Oquendo et al in 2004[13] studied 325 depressed patients to analyse the link with mild TBI and suicidal behaviour; 44% of the sample had mild TBI and suicidal behaviour was more common in this subgroup. Suicide Intent Scale and the Lethality Rating Scale was used to measure suicidal behaviour. However, exclusion of moderate to severe TBI and inclusion of only inpatients in this study would affect any generalisability of the results.

Case series: Psychiatric Disorders Following Brain Injury

Case 1- Patient A: Epilepsy, interictal psychosis and organic personality disorder following head injury

Patient A is a 37 year old female under mental health services with a diagnosis of organic personality disorder and interictal psychosis. She suffered from epilepsy from the age of 9 but coped well at school and went on to work successfully as a hairdresser. However, in 1998 at the age of 22 she was admitted to ITU with status epilepticus as a result of encephalitis of unknown cause, and remained severely unwell for several months. She recovered but was left with residual tonic clonic and complex partial seizures.

Since this episode, marked changes in her personality were noted. She developed mood swings with recurrent episodes of low mood, and expressed paranoid beliefs about people in the street talking about her. These beliefs resulted in her being agitated and physically aggressive, resulting in harm to both herself and others. She has required numerous admissions to acute wards and rehabilitation units because of her paranoid and suspicious behaviour and aggressive outbursts that her family were not able to manage in the community. She required restraint under Section 3 of the Mental Health Act in 2010, believing that care staff were poisoning her. Psychotic symptoms are most marked around seizures, with her displaying self-harming behaviour such as cutting off hair or painting face with nail polish. She frequently accuses staff and family of acting against her in these periods and her behaviour is very difficult to manage.

Her case has been challenging to manage successfully in the community by family and community teams, and she has needed several short and long term stays in acute wards and residential units. Her care has been coordinated jointly between neurological and psychiatric services. She currently lives with her parents and has carers to support her. Her epilepsy is yet to be successfully controlled; antipsychotics can lower the seizure threshold and so a delicate balance between these and her antiepileptic medication is warranted. There is an on-going concern that further mental health problems may develop in light of this.

Case 2- Patient B: Schizophrenia following head injury

Patient B is a 43 year old female with a diagnosis of schizophrenia, learning difficulties and epilepsy. She suffers from epilepsy in the form of absence and tonic-clonic seizures from the age of 7 months, when there is high suspicion that she sustained a head injury whilst in the care of extended family. Patient B has difficulties with numeracy and literacy, identified through psychological assessment, and an IQ of around 70. She has required three admissions under Section 2 of the MHA due to her paranoid delusions and poor self-care. Patient B frequently reports feeling monitored by cameras, suspicions that her food has been poisoned and that her personal belongings are being tampered with. She has attempted to take her own life due to feeling unable to cope with these delusions, laying in the road to be run over by a bus.

She is currently managed well in the community on oral risperidone for her psychosis and sodium valproate for her epilepsy; she resides in supported accommodation and has required stints in long term residential and rehabilitation beds due to her mental health problems and learning difficulties.

Case 3- Patient C: Depression and Personality disorder after head injury

Patient C first came in to contact with psychiatric services in 2007 and was diagnosed with depression and organic personality disorder. At the age of 16 this gentleman was knocked off his bicycle and sustained a severe head injury, from which he was left in a coma for over three weeks, but recovered well enough to go home. In 1994 he started having blackouts, was investigated extensively by neurology, and diagnosed with

non-epileptic attack disorder. As part of these investigations, Patient C underwent an MRI which demonstrated significant brain damage including traumatic damage to the frontal lobes. This was likely due to his accident at age 16. From his first assessment by psychiatric services, he eluded to thoughts and behaviours that were of serious concern to his team. He reported feeling emotionally detached from his family, gaining little pleasure from life, getting in to fights frequently and allegedly having stabbed someone in an altercation several years ago. He described to practitioners only getting excitement out of reading and watching programmes about serial killers, and occasionally became sexually aroused by this. He had made extensive written plans on how he would capture, torture and kill the couple he believed were responsible for his accident at 16. He also struggles with auditory command hallucinations telling him to harm himself and others. He frequently self harms, often using a Stanley knife to cut his arms and legs. Patient C has been jointly managed by adult psychiatry and neuropsychiatry on an outpatient basis. His risks of aggression and violence have been carefully managed through regular assessment and involvement of forensic services.

Conclusion:

The literature search indicates that the prevalence of psychiatric disorders in patients with brain injury is much higher compared to general population. The significance of the results are however greatly affected by response bias, the impact of patients' cognitive impairment on their study participation, observer biases and the small study population sizes; however, we believe that these short-fallings should be seen as a trigger to stimulate more comprehensive and wide-scale research in to this field. The methodologies used by authors described in the literature review demonstrate the wide variance in the tools used to assess psychiatric illness in patients following TBI; we therefore argue that universal case definitions need to be agreed on and implemented to standardise studies and reduce bias. The economic impacts and impacts on quality of life have often been neglected by researchers and warrant formal assessment. From a service delivery perspective, rehabilitation programs need to identify patients with signs of psychiatric illness post TBI earlier and involve psychiatric service in the development of integrated care plans to improve the total outcome and quality of life of the patient. The impact on the patient's family and carers also need to be explored further to provide an evidence base for more effective and holistic interventions.

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Case Report

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Cholestatic hepatitis: An unusual presentation of lisinopril induced hepatotoxicity

Gurpinder Singh, Amit Kachalia, Jaspreet Kaur, Kinjal Kachalia, Shaojun Liu and Vincent Rizzo

Abstract

Previously published case reports have shown direct hepatocellular injury as the mechanism for lisinopril induced hepatotoxicity. We report case of a 47 year old female who presented with jaundice, diagnosed as cholestatic hepatitis;two years after initiation of lisinopril. Extensive work up was negative for other causes of hepatitis. Liver biopsy showed portal inflammation by lymphocytes without centrilobular necrosis, which is similar to earlier case reports. Discontinuation of angiotensin converting enzyme inhibitors (ACE-I) usually leads to normalization of liver enzymes, however continuation or re-initiation can be potentially fatal.

This is the first reported case of lisinopril induced hepatotoxicity via cholestatic mechanism. Some reports hypothesize a metabolic idiosyncratic reaction as the molecular mechanism but currently there is no validated literature. This case highlights the need for further research to explore mechanisms for ACE-I mediated hepatotoxicity and to create awareness amongst physicians to consider ACE-I as an etiology for drug induced liver injury.

Keywords: Angiotensin coverting enzyme inhibitor, Hepatotoxicity, Cholestatic hepatitis, Lisinopril

Abbreviations: ACE-I: Angiotensin converting enzyme inhibitors; DILI: Drug induced liver injury; AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma-glutamyl transferase; ALP: Alkaline phosphatase; ANA: Anti nuclear antibody; AMA: Anti mitochondrial antibody; ANCA: Anti-neutrophil cytoplasmic antibody; CKD: Chronic kidney disease

Introduction:

Various classes of medications have been known to cause drug induced liver injury (DILI), however not much literature has been published regarding angiotensin converting enzyme inhibitors (ACE-I) causing DILI. Recent years have seen tremendous increases in ACE-I prescriptions for coronary artery disease, diabetic nephropathy and hypertension. We report the first case of lisinopril induced hepatitis via a cholestatic mechanism.

Case:

A 47 year old female with history of diabetes mellitus type 2, hypertension, chronic kidney disease (CKD)stage III, non-obstructive coronary artery disease was admitted with complains of generalized weakness, lack of appetite, yellow discoloration of skin and eyes, dark urine and white stools for 1 week prior to admission. She denied history of alcohol abuse, past liver disease, illicit drug use, recent sick contacts, fever, chills, travel. Current patient medications included lisinopril, pioglitazone, furosemide, atenolol, metformin and detemir. Patient was started on these medications about 2 years prior to admission. Patient received enalapril for 5 months before switching to lisinopril about 2 years prior to presentation.

Physical examination was positive for icteric sclera, icteric skin; negative for spider nevi, palmar erythema and asterixis. Exam did not reveal hepatomegaly or splenomegaly. Labs showed hemoglobin 8.7 gm/dl, normal white count and platelet, normal C-reactive protein, alkaline phosphatase (ALP) 750 U/L, aspartate transaminase (AST) 169 U/L, alanine transaminase (ALT) 210 U/L, gamma-glutamyl transferase (GGT) 813 U/L, total bilirubin 13.4mg/dl with conjugated fraction 7.7mg/dl, ammonia level 64. Prior to initiation of lisinopril ALP was 87 U/L, GGT 53 U/L, with AST18 U/L, ALT 11 U/L and normal bilirubin fractions. Hepatitis A, B, C and D serologies were negative. Serum acetaminophen level was normal. Anti nuclear antibody (ANA), anti- mitochondrial antibody (AMA), anti-endomysial antibody, c-anti-neutrophil cytoplasmic antibody (ANCA), p-ANCA was negative. Anti smooth muscle antibody was weakly positive in titre of 1: 40. Creatine kinase, ceruloplasmin and alpha -1 antitrypsin level were normal. Quantiferon gold was negative. Lipid panel was deranged with cholesterol level 1017 and low density lipoprotein 1006, triglycerides 255.

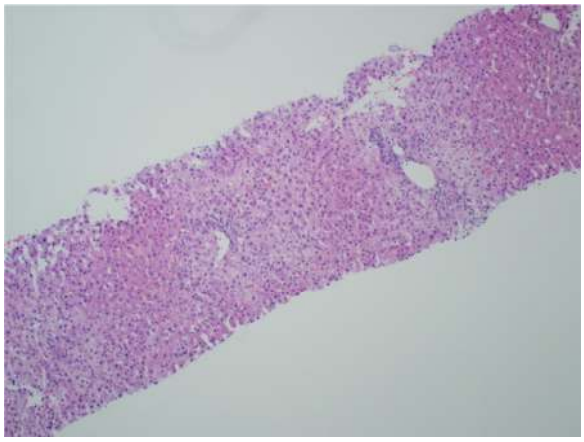

Figure 1: Mild hepatitis with portal tract lymphocytic infiltration

Ultrasonography and magnetic resonance imaging abdomen showed hepatomegaly 17.5cms but was negative for fatty infiltration of liver, stones, cirrhotic features or dilation of biliary tree. Liver biopsy was done which showed mild portal chronic hepatitis with lymphocytic infiltration (Fig: 1), cholestasis (Fig: 2), mild portal fibrosis (Fig: 3), negative for bile duct damage (Fig: 4), negative for cytoplasmic inclusion. Congo red stain was negative for amyloid.

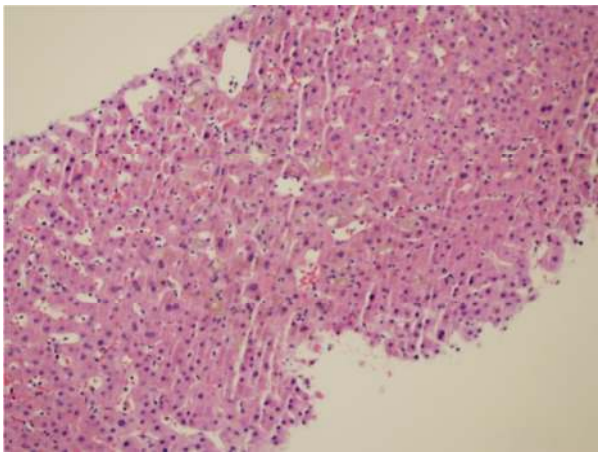

Figure 2: Cholestasis.

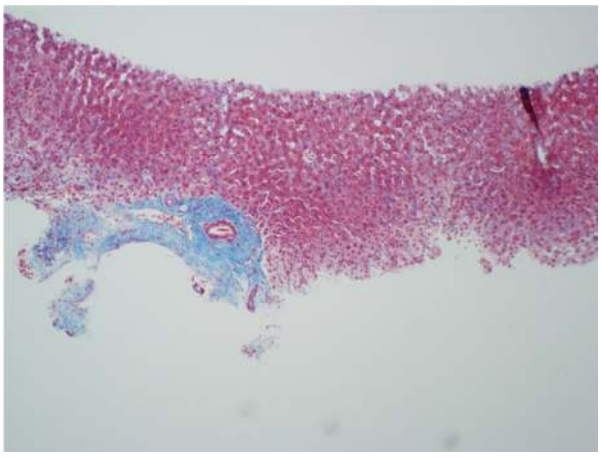

Figure 3: Trichrome stain showing portal tract fibrosis.

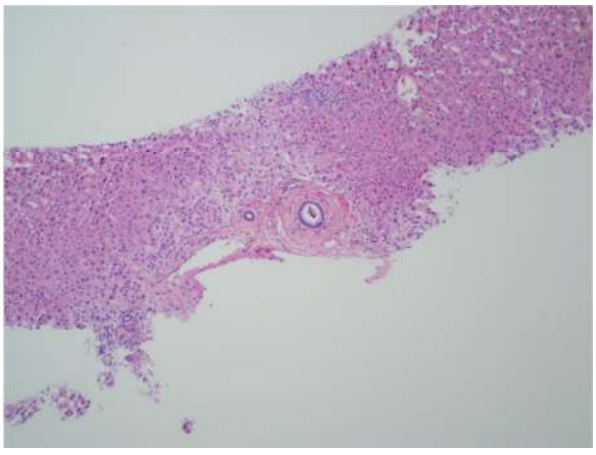

Figure 4: Normal bile ducts in portal tract.

Patient was treated with fluids, anti-histaminic, ursodeoxycholic acid. Patient was unable to tolerate coleveselam. Impression was drug induced hepatitis, lisinopril was discontinued and patient improved clinically and biochemically. Discharge labs two weeks after discontinuation of lisinopril showed AST 80 U/L, ALT 70 U/L, ALP 1045 U/L and GGT 1212 U/L; total bilirubin of 3.93 mg/dl with conjugated fraction 2.43mg/dl. Patient was discharged uneventfully with follow up in Hepatology clinic. Six months after discontinuation of lisinopril ALP was 199 U/L, GGT 168 U/L with AST 19 U/L, ALT 17 U/L, total bilirubin 0.9mg/dl and conjugated bilirubin 0.21mg/dl. Patient is currently asymptomatic and icterus has resolved.

Discussion:

ACE-I has been used widely for coronary artery disease, hypertension and diabetic nephropathy and approximately 159 million prescriptions for ACE-I are written annually. Recent JNCC guidelines recommended ACE-I to be used as first line anti-hypertensives for patients with CKD and diabetes. The common side effects known about ACE-I use are cough and angioedema, hypersensitivity. However not much awareness exists regarding ACE-I induced hepatotoxicity. It is important to consider ACE-I as an etiology for drug-induced liver injury (DILI) since continuation of the ACE-I beyond onset of hepatitis is fatal[1].

Literature review shows multiple reports of DILI with captopril[2, 3], ramipril[4], fosinopril[5, 6] and enalapril.[2,7] Most commonly implicated ACE-I are enalapril and captopril. The usual presentation for ACE-I induced hepatotoxicity is cholestasis mediated hepatitis. Till date there have been four case reports published reporting lisinopril as cause of hepatitis [1, 8, 9] All 4 cases of lisinopril induced hepatotoxicity have shown a hepatocellular pattern of liver injury and did not show any cholestatic features. We report the first case of lisinopril induced cholestasis mediated hepatotoxicity.

In our case, patient had received enalapril for 5 months before initiation of lisinopril; however patient developed symptoms 2 years after initiation of lisinopril. The patient had no past medical history of liver or biliary tract disease. A thorough investigative workup was negative for autoimmune and other viral causes of hepatitis. Older case reports of lisinopril induced toxicity have shown similar histopathological findings of portal inflammation by lymphocytes without centrilobular zonal necrosis.[9] There are various theories regarding possible mechanisms for DILI with lisinopril, namely terminal proline ring mediated bile stasis[8, 10] and hypersensitivity to the sulfhydryl group.[2] Discontinuation of metformin, pioglitazone, furosemide, atenolol and detemir did not result in clinical or biochemical improvement. Patient was initially continued on lisinopril since suspicion was low and then later discontinued. Similarity in histopathological findings along with a strong temporal relationship between lisinopril withdrawal and improved biochemical and clinical scenario, with absence of other constitutional symptoms and eosinophilia strongly point toward lisinopril-induced hepatotoxicity.

Our case had a long period of latency between drug intake and onset of hepatic injury which is consistent with other published reports of lisinopril induced hepatocellular injury[9, 10, 11]; however the mechanism responsible for latency or hepatotoxicity remains unclear. Earlier report postulate metabolic idiosyncratic reaction as a possible molecular mechanism for hepatocellular injury[9]. However our case is unique as the primary mode of injury appears to be cholestatic. Since our patient received enalapril before initiation of lisinopril without any adverse events, this case adds further controversy as to whether this patient could have been safely continued on other ACE-I except lisinopril or whether she would have developed hepatotoxicity if enalapril was continued. This case highlights further need for research to evaluate ACE-I induced hepatotoxicity. Currently the awareness for ACE-I induced liver injury is low and there are no guidelines guiding physician to monitor for possible hepatic adverse events. Further research is needed to delineate the mechanism by which ACE-I cause hepatotoxicity and to define possible risk factors.

Conclusion:

Discontinuation of ACE-I beyond recognition of DILI hepatitis usually leads to normalization of liver enzymes, however continuing or reinitiating ACE-I can be severe and potentially fatal. Thus, it is important to be aware of ACE-I as a possible cause of DILI, which can present with either hepatocellular or cholestatic mechanism and to promptly discontinue ACE inhibitor use. Currently there are no guidelines in place for monitoring of liver enzymes following initiation of ACE-I and more research is required to delineate possible mechanisms and prevent further DILI in such patients.

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Research Article

Content and Timing of Inpatient Discharge Summaries at the Mount

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Abstract

Aim: The discharge summary is a vital component of patient care. It is a means by which information is conveyed to clinicians and community mental health team who will be involved in follow-up patient care. This calls for accuracy as well as completeness of information as these are vital components that can directly impact patient care. Timing of discharge letter/summary reaching the follow-up physician, general practitioner or community mental health team, from point of discharge can also play a key role in patient management. This audit looks at the content and timing of discharge summaries from The Mount, Old Age Psychiatry hospital as to whether it adheres to the local Trust guidelines.

Methods: Discharge summaries from electronic database were reviewed. In cycle 1 of the audit, adherence to local Trust guidelines in relation to the content, accuracy and timing of discharge summaries were studied. In the follow-up audit cycle, changes in clinical practice brought about following recommendations were studied.

Results: Recommendations and feedback were found to be effective in significantly improving adherence to inclusion of family history ($p<0.001$), social history ($p<0.001$), premorbid history ($p=0.036$), progress and treatment during hospital stay ($p=0.049$) in the discharge summary. Significant decrease was observed in inclusion of follow-up arrangements ($p=0.007$). Other significant improvements included lesser spelling errors ($p<0.001$), dictation ($p<0.001$) and typing ($p<0.001$) of discharge letter within 5 working days of discharge of patient.

Conclusions: This study adds to importance of accuracy and timing of discharge summaries to ensure good medical practice and continuity of care. It also establishes scope for improvement and recommendations that can further improve clinical practice. Furthermore, key decisions on patient care can be made by follow-up health professionals, at the earliest and with the help of appropriate information.

Introduction

The discharge summary is an integral part of continuing patient care. Apart from containing vital information regarding current admission, it also conveys key findings and plans to clinicians who will be taking over the care of the patient. This would mean communicating important information about patients to ensure appropriate and safe follow-up management. Studies involving discharge summaries have looked into role of communication from secondary to primary care and have highlighted the importance of accuracy and quality of information,[1] errors[2] and general practitioner (GP) preference.[3] Systematic reviews have found low availability (12-34%) of discharge summary during first visit post-discharge as well as wide variations in content of discharge summaries thereby directly affecting patient management.[4,5] The timing of discharge summary completion and reaching the follow-up physician is therefore of prime importance wherein this has been also found to influence and reduce the risk of rehospitalisation.[6] The content necessary for a 'good' or 'high-quality' discharge summary has been studied via surveys. The inclusion of important data such as diagnosis, discharge drugs, complications, laboratory results and follow-up plans have been considered to be important clinical information by hospital physicians and GPs.[7]

Hospital discharge summaries can be hand-written, dictated or in electronic format. These formats have their benefits and downfalls. Hand-written summaries have been found to be well-accepted by primary care physicians although involve the factor of legibility.[8] A randomised-controlled trial found no difference between electronic and dictated discharge summaries for primary care physician satisfaction.[9] Although the use of electronic discharge summaries has significantly improved both the content and timing of discharge summaries reaching follow-up physician or healthcare staff,[10] they have been found to contain higher number of errors in patient progress, additional diagnosis and free-text components.[11]

This audit examined the timing and content of discharge summaries at The Mount and whether they met local Trust standards. A follow-on audit was conducted to study the impact of recommendations that had been put forward at the end of Cycle 1 of the audit.

Aim and Objectives

Aim

Cycle 1: To study the content, accuracy and timing of discharge summaries at The Mount, Old Age Psychiatry hospital.
Cycle 2: To examine changes in clinical practice following recommendations from Cycle 1 of audit involving content and timing of discharge summaries from The Mount.

Objectives

Cycle 1: To ascertain whether Trust guidelines regarding content of discharge summaries are met and also whether the timeline guidance is being maintained.

Cycle 2: To examine adherence to the Trust guidelines as well as to study the changes brought about by recommendations at the end of Cycle 1.

Criteria/ Standards

Trust guidelines state:

- Discharge summaries must be typed and sent in 5 working days post-discharge from hospital.
- They must include the following information (Box 1):

Box 1 Trust guidelines for inclusion of information in discharge summaries

Patient ID
Date dictated
Patient Name
Date of Birth
Name of consultant
Admission address
Discharge address
Admission date
Discharge date
Reasons for admission
History of present illness
Past medical history
Past psychiatric history
Family history
Social history
Occupational history
Premorbid history
Mental health examination
Physical examination
Results of investigations
Progress & treatment during admission
Final diagnosis
Discharge medications
Follow-up arrangements
Name of key worker
Number of pages

Method

Audit Sample: Patients admitted and discharged from Ward 3 & 4 of The Mount, between 01.04.2011 to 31.10.2011. A total of 103 patient discharge summaries were therefore analysed in Cycle 1 of the study. For cycle 2, the audit sample comprised of patients admitted and discharged from Ward 3 & 4 of The Mount, between 01.04.2012 to 31.10.2012. A total of 97 patient discharge summaries were therefore analysed in this part of the study.

Data Collection: Data was collected using an anonymous data collection tool (Appendix 1) which was designed according to Trust guidelines. Administrative staff provided the clinical audit leads with list of patients discharged during the study dates. The electronic patient record system of the Trust (PARIS: Patient Record Information System) was used to study the discharge summary letters. Data collection was performed under the supervision of consultant responsible for the audit, between November 2011 and January 2012 for cycle 1 and for cycle 2 data collection was performed between October 2013 and November 2013. Patient confidentiality and anonymity was maintained.

Data Analysis: Qualitative data was gathered, coded and collated on to a Microsoft Excel spread sheet. The data collected was reviewed by the authors to ensure each aspect of data collection tool was filled. The data was analysed by the Clinical Audits Facilitator at the Trust Clinical Audit Support Team and placed into a report format for dissemination.

Results

The number of discharge summaries analysed in Cycle 1 and 2 of this study was 103 and 97 respectively.

Data were collected using the data collection tool (appendix 1). Dates of discharge, dictation and typing were recorded. Date of typing was used as a proxy of date sent to GP since there was no record of this. Seven days were permitted for discharges to be sent (equivalent to 5 working days). Discharge summaries were read and it was recorded if each stipulated heading from the Trust guidelines was present. No comment was made on quality of information; only consideration was whether information was present or absent.

Compliance with each point from the above categories is shown in the following series of tables and comparison is made between the studies in Cycles 1 and 2 (Table 1-4). The statistical significance of the differences found in the two audit cycles was evaluated using chi-square tests.

The comparison of findings from Cycle 1 and 2 establish a significant increase in adherence to family history ($p<0.001$), social history ($p<0.001$), premorbid history ($p=0.036$) as well as progress and treatment during hospital stay ($p=0.049$) components of the discharge summary. There was also a significant increase in inclusion of date of dictation of discharge summaries ($p<0.001$). Increase in adherence to most of the components of discharge summaries was observed. However, there was significant decrease in inclusion of follow-up arrangements ($p=0.007$) as well as a decrease in inclusion of name of key-worker assigned to patient (from 64% in cycle 1 to 56% in cycle 2; $p=0.0225$). A significant decrease in spelling/typing errors in diagnosis or medical jargon was observed ($p<0.001$).

Table 1 Presence of information on discharge summary according to Trust guidelines

Criteria	Adherence % 2011 (n=103)	Adherence % 2013 (n=97)	Statistical significance
Patient code	100% (n=103)	97% (n=94)	p=0.721
Date dictated	72% (n=74)	98% (n=95)	p<0.001
Patient Name	100% (n=103)	100% (n=97)	No change
Date of birth	97% (n=100)	100% (n=97)	p=0.090
Name of consultant	98% (n=101)	99% (n=96)	p=0.596
Name of current GP	98% (n=101)	98% (n=95)	No change
Admission address	98% (n=101)	100% (n=97)	p=0.167
Discharge address	98% (n=101)	100% (n=97)	p=0.167
Admission date	97% (n=100)	100% (n=97)	p=0.090
Discharge date	97% (n=100)	99% (n=96)	p=0.342
Legal status	99% (n=102)	98% (n=95)	p=0.525
Reasons for admission	98% (n=101)	98% (n=95)	No change
History of present illness	100% (n=103)	99% (n=96)	p=0.301
Past medical history	89% (n=92)	95% (n=92)	p=0.150
Past psychiatric history	95% (n=98)	98% (n=95)	p=0.282
Family history	19% (n=20)	86% (n=83)	p<0.001
Social history	56% (n=58)	89% (n=86)	p<0.001
Occupational history	67% (n=69)	68% (n=66)	p=0.873
Premorbid history	37% (n=38)	52% (n=50)	p=0.036
Mental health examination	95% (n=98)	93% (n=90)	p=0.482
Physical examination	86% (n=89)	92% (n=89)	p=0.227
Results of investigations	84% (n=87)	78% (n=76)	p=0.265
Progress & treatment during admission	96% (n=99)	100% (n=97)	p=0.049
Final diagnosis	92% (n=95)	97% (n=94)	p=0.147
Discharge medications	98% (n=101)	97% (n=94)	p=0.602
Follow-up arrangements	86% (n=89)	79% (n=77)	p=0.007
Name of key worker	64% (n=66)	56% (n=54)	p=0.225
Number of pages	0% (n=0)	0% (n=0)	No change
Are there any spelling/typing errors in the list of medications?	90% (n=8)	98% (n=2)	p=0.064
Are there any spelling/typing errors in the diagnosis and medical terminology?	78% (n=21)	99% (n=1)	p<0.001

Table 1: The presence of information mentioned in the Trust guidelines is analysed. The percentage adherence in cycle 1 is compared with findings from cycle 2. Significant increase in inclusion of family history, social history, follow-up arrangements and date of dictation is observed. A healthy increase is also observed in inclusion of premorbid history and progression and treatment during admission. A significant reduction in spelling/typing errors is also seen. The decrease in inclusion of name of key worker, discharge medications, mental health examination and results of investigation amongst others is also noted. GP, general practitioner.

Timing of Discharge Summaries

The number of discharge summaries being dictated and typed within 7 days of discharge was significantly increased (p<0.001) and a significant decrease in discharge letters being dictated more than 2 weeks (p=0.004) or 3 weeks (p<0.001) of patient being discharged was observed. The time taken between dictation of letter and it being typed up was also found to have dropped, with 73% being done within 7 days, significant decrease (p<0.001) being observed since the first cycle.

Furthermore, a significant increase is observed in early (less than 7 days) typing of discharge letter since patient being discharged (p<0.001).

Table 2 Time taken between discharge of patient and dictation of letter

Days	Adherence % 2011 (n=74)	Adherence % 2013 (n=94)	Statistical significance
0-7	30% (n=22)	73% (n=69)	p<0.001
8-15	24% (n=18)	22% (n=21)	p=0.762
16-22	18% (n=13)	4% (n=4)	p=0.004
23+	29% (n=21)	0% (n=0)	p<0.001

Table 2: The time taken between discharge of patient and dictation of letter is analysed. A significant increase is observed in the dictation of letter as per Trust guidelines (within 5 working days).

Table 3 Time taken between dictation and typing of discharge letter

Days	Adherence % 2011(n=75)	Adherence % 2013 (n=94)	Statistical significance
0-5	84% (n=63)	73% (n=69)	p<0.001
6-11	7% (n=5)	24% (n=23)	p=0.192
12+	9% (n=7)	2% (n=2)	p<0.001

Table 3: The time taken between dictation of letter and typing of discharge letter is analysed. A significant decrease is observed in the time taken for typing of letter within 5 days of dictation of letter.

Table 4 Time take between discharge and typing of discharge letter

Days	Adherence % 2011 (n=100)	Adherence % 2013 (n=96)	Statistical significance
0-7	18% (n=18)	52% (n=50)	p<0.001
8-15	32% (n=32)	34% (n=33)	p=0.724
16+	60% (n=60)	14% (n=13)	p<0.001

Table 4: The time taken between discharge of patient and typing of discharge letter is analysed. A significant increase is observed in the early typing of discharge letter from the date of discharge of patient.

Discussion:

The discharge summary is a very important means to communicate medical (both physical and psychiatric) and nursing interventions to the GP or community mental health team. This in turn helps in making invaluable decisions to patient care in the community. Hence, it is worth spending time on doing a good discharge letter which includes relevant information. A timely discharge letter can also be very useful in this regard.

At the end of Cycle 1 of the audit, recommendations that were made included (Appendix 2):

- Disseminating information amongst all junior doctors, consultants and administrative staff on each ward to include the above mentioned headings in accordance with Trust guidelines.
- Information was also provided regarding finding out Name of Keyworker in PARIS system.
- A specific note was also placed regarding to spell out medical terminologies that would assist in the typing of discharge summaries by administrative staff.

From the results, it is evident that the content of the discharge summary has largely been maintained. In other words, good practice was maintained and recommendations from previous audit were implemented in most spheres of discharge letters. However, despite the recommendation of finding out name of key-worker from PARIS system, there was a decrease (from 64% in first cycle to 56% in second cycle) in its inclusion (p=0.225). Thus, training in usage of information technology system is essential. Providing appropriate instruction and training to junior doctors has been found to be useful in improving the quality of discharge summaries.[12] Therefore, it might be beneficial to include instructions or guidelines for appropriate discharge summaries at local Trust or departmental inductions. This will help junior doctors in ensuring completion of accurate and succinct discharge summaries that will aid in patient management.

There was a reduction in documentation of discharge medication, follow up arrangement, mental state examination and physical health investigation carried out as an in-patient. This certainly needs improving as these are the relevant areas to facilitate smooth transition of care in the community and follow-up arrangement. With regard to the timing of the discharge summary, this was found to have significantly improved from the previous audit cycle. For example, the timing between discharge and dictation (within 7 days) has increased from 30% to 73% and almost all discharge summaries are dictated no later than 3 weeks. The possible reasons for delays in dictation could be ongoing workload, availability of medical staff and of the medical notes, as these are sometimes requested by the Intermediate Community Service (ICS) team. There was a slight drop in the time between dictation and typing (from 84% to 73%), which could possibly due to availability of administrative staff, dictation tapes or medical notes and proof reading by medical staff. Significant increase was observed in inclusion of date of dictation of discharge summaries which will be a useful component for future audits.

A significant decrease in spelling/typing errors in diagnosis or medical terminologies was observed. Furthermore, there was significant increase in inclusion of family history, social history, premorbid history as well as information on progress and treatment during hospital in the discharge summary. Therefore, timely audit and feedback can be very useful in improvement of discharge summaries and patient care.

Recommendations & Actions:

1. Raise awareness amongst senior house officers (SHO's) and other doctors in the Trust regarding recording of pre-morbid history, occupational history, name of keyworker as this was only done in 52%, 62%, 56% cases respectively. This could be done by disseminating findings from this audit amongst SHO's and other doctors of Trust through hand-outs to wards as well as through local teaching session.
2. Remove number of pages from the list of sub-headings needed in discharge summary as this is dependent on typing and not necessarily possible to estimate while dictating discharge summary. However, it is an important part of discharge summary. Therefore, send information with audit findings to medical secretaries informing the need to keep number of pages in the discharge summary.
3. Consider adding a section on documentation of risk assessment should be included in the discharge summary as well as 'early relapse signature' which would enable early intervention in the community to avoid inpatient admission. This could be included in the discharge summary. This would involve liaising with consultants and the responsible person for making/printing discharge summaries for Trust.

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None declared
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Appendix 1: Data Collection Tool

0082 - Discharge Summary Audit

Leeds Partnerships NHS
NHS Foundation Trust

Project 0082 - An Audit of the Content and Timing of Inpatient Discharge Summaries at The Mount

Date of discharge d d m m y y y y

Date of dictation d d m m y y y y

Date typed d d m m y y y y

Is the following information present on the Discharge Summary?

1.	Patient Code	Yes / No	11.	Legal Status	Yes / No	21.	Physical Examination	Yes / No
2.	Date Dictated	Yes / No	12.	Reasons for Admission	Yes / No	22.	Results of Investigations	Yes / No
3.	Patient Name	Yes / No	13.	History of Present Illness	Yes / No	23.	Progress & Treatment during Admission	Yes / No
4.	Date of Birth	Yes / No	14.	Past Medical History	Yes / No	24.	Final Diagnosis	Yes / No
5.	Name of Consultant	Yes / No	15.	Past Pschiatric History	Yes / No	25.	Discharge Medications	Yes / No
6.	Name of Current GP	Yes / No	16.	Family History	Yes / No	26.	Follow-up Arrangements	Yes / No
7.	Admission Address	Yes / No	17.	Social History	Yes / No	27.	Name of Key Worker	Yes / No
8.	Discharge Address	Yes / No	18.	Occupational History	Yes / No	28.	Number of Pages	Yes / No
9.	Admission Date	Yes / No	19.	Premorbid Personality	Yes / No			
10.	Discharge Date	Yes / No	20.	Mental Health Examination	Yes / No			

29. Are there any spelling/typing errors in the list of medications? Yes / No

30. Are there any spelling/typing errors in the diagnosis and medical terminology? Yes / No

1 of 1

Appendix 2 (Cycle 1 recommendation leaflet)

Information for Junior Doctors re Discharge Summaries at The Mount (2012)

Trust guidelines state that all discharge summaries should be sent to GPs within 5 working days of discharge.

Discharge summaries have to be dictated by yourselves, typed by administrative staff and checked by consultants before being sent out so to meet the target they need to be dictated **on the day of discharge or the day after discharge at the latest**. This is regularly audited.

To find out name of **key worker (Care Coordinator)**, go to Central Index on PARIS, then 'Involved staff'. This information, and follow up arrangements, must be included in the discharge summary.

If you are using medical jargon please spell it out to assist administrative staff.

The following information should be included in discharge summaries (according to Trust guidelines):

1. Patient Code:
2. Date dictated:
3. Patient Name:
4. Date of Birth:
5. Name of Consultant:
6. Name of Current GP:
7. Admission Address:
8. Discharge Address:
9. Admission date:
10. Discharge date:
11. Legal Status:
12. Reasons for admission:
13. History of present illness:
14. Past medical history:
15. Past Psychiatrist history:
16. Family History:
17. Social history:
18. Occupational history:
19. Premorbid Personality:
20. Mental state Examination:
21. Physical examination:
22. Results of Investigations:
23. Progress & treatment during admission:
24. Final diagnosis:
25. Discharge Medications:
26. Follow-up arrangements:
27. Name of Key worker:
28. Number of pages