Cognitive processes across anxiety disorders related to intolerance of uncertainty: Clinical review

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Abstract: Objective: Being a relatively recent concept, the intolerance of uncertainty (IU) suffers from inconsistent definitions and conceptual overlap. The core objective of the study is to clarify its clinical manifestations and its involved cognitive processes. Method: The procedure is based on algorithms (equations of keywords) encoded simultaneously in databases (Scopus, PubMed, and PsycArticles). Results are filtered by the year (range of 10 years [2005–2015] because it is a recent concept) and the relevance of abstracts. Once the studies are appraised, results are categorized in two groups: studies which examine the IU in a clinical perspective (relations with one or several anxiety disorders) (cluster A) and those which measure the IU through a cognitive perspective (cognition, metacognition) (cluster B). Results: 66 results are retrieved: 50 results concern the cluster A and 16 examine the cluster B. The state of the IU varies between studies (e.g. predictor and mediator), which make comparisons difficult. Notwithstanding, the IU construct seems to be a broad transdiagnostic maintaining risk factor involved in a range of psychological disorders. Conclusion: This clustering supported that researchers and clinicians may benefit from incorporating IU within cognitive and computational research design and as a specific treatment target.

ABOUT THE AUTHORS

Our laboratory participates in psychologists’ formation in the field of the health psychology and its specificities. Our researchers and clinicians develop research projects and clinical activities in the field of the emergencies, the quality of life, the chronic diseases, the anxiety and the psycho-oncology in children and adults. This study integrates the psychology-oncology axis and takes root in other related themes of the laboratory such as the anxiety (related with intolerance of uncertainty and its components) and the quality of life in parents of child cancer survivor. This project is approved by all of Ethics Committees and is led in Belgian hospitals.

PUBLIC INTEREST STATEMENT

Who was not ever worried about a situation or event of the everyday life? When we are worried about a situation, we feel hesitating, uncomfortable or anxious. Nevertheless, worries and uncertainties are normal phenomena of the individual (the life is full of uncertainties). For some individuals, they tend to be extremely "allergic" to uncertain events. Those individuals are called "intolerant of uncertainty". This phenomenon is observed as a personality’s characteristic that may leads to distress for the individual (anxiety, depression ...) and impacts her/his quality of life. The study aims to investigate the state of the literature on the intolerance of uncertainty and especially their relation with psychological distress (the anxiety and the depression). Results show evidence that the intolerance of uncertainty could give rise to several psychological distresses and may impair diverse individual’s skills such as the resolution of daily problem or still mental strategies to cope with uncertain event. Note that Marie Vander Haegen has been set as corresponding author, since she is the first author.
1. Review outline and aims
The current study sought to advance understanding of IU through a review of its relations to symptoms of anxiety disorders; namely generalized anxiety disorder (GAD), obsessive-compulsive disorder (OCD) and its cognitive processes. The originality of this review lies in considering the psychopathological and cognitive perspectives of IU. Indeed, previous studies examined either the pathological links with the UI, or the cognitive processes involved in the UI.

The aim of the study is the examination of the relations between IU and anxiety disorders and also its involved cognitive components. Two gradual steps are proposed in order to achieve the aim. The first step is to estimate the association of IU with GAD and OCD and its clinical aspects. The second step is to examine the cognitive components of IU. Methodological strengths and weaknesses of empirical studies in the IU’s area are argued in the “discussion section”.

Increasing interest for IU in understanding psychopathology has boomed in recent decades. In spite of a flourishing literature of anxiety disorders, few have examined the cognitive state of the IU across anxiety disorders. The organization of the clinical review is divided into two major theme parts as follows: IU and Anxiety Disorders Perspective (cluster A) and IU and Cognitive Processes Perspective (cluster B). It is mentioned that each cluster brings together research involving either clinical variables (i.e. solely an advanced clinical hypothesis) or cognitive variables (i.e. solely an advanced cognitive hypothesis).

The outline of this review is as follows: first, we provide background material delineating IU and its correlates but also, the core cognitive elements in anxiety disorders; we review the algorithmic method and its statistical outcomes. Based on this, we provide a critical review of the current state of research led in the domain and how IU activates through clinical and cognitive perspectives. Future research avenues about IU construct are proposed in the “discussion section”.

2. Theoretical framework
2.1. Uncertainty until a certain acceptable point
The state of uncertainty is seen as a realization that our beliefs and representations of the world are unable to accurately predict future events in our environment. Despite the normal state of uncertainty (i.e. life is full of uncertainties), empirical evidence supports that uncertainty is a significant stressor involving physiological and psychological consequences for the individual (Rosen, Ivanova, & Knäuper, 2013; Zlomke & Jeter, 2014).

In contrast, IU refers to a trait of the individual (dispositional risk factor developed during childhood) rather than a perceived characteristic of the event (Zentner & Bates, 2008). IU is observed as a set of negative cognitive, emotional and behavioural reactions to situational uncertainty. Researchers have defined IU as a single construct made up of four dimensions: (1) individual perceives that uncertainty upsetting and stressful, (2) attributes it is an intolerable situation and should be avoided, (3) conceives that uncertainty is unfair and (4) lead to an inability to act (Robichaud, 2013).

In other words, for the same situational uncertainty, two individuals with identical perceptions of occurrence and consequences may differ in their threshold of tolerance of uncertainty towards the situation (Freeston, Rhéaume, Letarte, Dugas, & Ladouceur, 1994). For example, an individual who is intolerant of uncertainty would evaluate the situation as being more disturbing, and tend to view...
uncertainty as threatening, and overwhelming whereas an individual who is not intolerant of uncertainty would evaluate the situation less disturbing and may view uncertainty as solvable and acceptable.

Empirical studies observed that individuals who are intolerant of uncertainty will perceive more many sources of danger in their daily life and have more reactions of hypervigilance when they are faced with uncertain or ambiguous situations (Dugas, Burh, & Ladouceur, 2004; Nelson & Shankman, 2011).

2.2. Anxiety disorders: cognitive perspective
Anxiety disorders form a category (DSM V code: 300.00; American Psychiatric Association, 2013) of mental pathologies that are characterized by overwhelming feelings of panic and fear, uncontrollable intrusive thoughts, painful and intrusive memories, excessive worries, sleep disturbance and somatic symptoms (e.g. muscle tension, stomach disorders, heart pounding ...). Anxiety disorders share a continuum of symptoms (comorbid pathology) with other pathologies, especially major depressive disorders (MDD). Moreover, they are often recurring in nature and impaired quality of life (e.g. personal distress, substance abuse, greater mortality, suicide risk factor) (Garner, Möhler, Stein, Mueggler, & Baldwin, 2009).

Cognitive theorists (e.g. Hallion & Ruscio, 2011) propose that biases and dysfunctions are frequently reported in anxiety disorders. Distorted thoughts about the dangerousness of certain situations/events or sensations are the most preponderant outcomes. The observations of these biases have been highlighted in several cognitive tasks (e.g. the modified Stroop task, the spatial cueing task, the dot probe task) suggesting that the phenomenon is not an artefact of the particular situation procedures (for a review see MacLeod & Mathews, 2012). Some explanations of these attentional biases have put forward.

Two types of processes or systems typically one more automatic (affective/motivational) and one more controlled (calculating/deliberative) are recognized in cognitive models. The so-called dual-process model differentiates the “cold” from the “hot” cognition. The “cold cognition” concerns the self-control; encompasses automatic processes, and is more slow, reflective and complex. Conversely, the “hot cognition” refers to a system encompassing affective and motivational processes that are affect-charged (affective processes themselves as well as a phenomenon such as emotional appraisal) (David & Szentagotai, 2006; Prencipe et al., 2011). Several cognitive domains of dysfunction in anxiety disorders are reported in the literature; mainly cold and hot cognition deficits.

2.2.1. Cold cognition deficits in anxiety disorders

2.2.1.1. Executive functions and attentional process. The former category concerns disproportionate attention allocation to threatening stimuli in anxious disorders (Eysenck, Derakshan, Santos, & Calvo, 2007). Cisler and Koster (2010) located three core elements of attentional bias: (1) facilitated attentional deployment, (2) the attentional disengagement and (3) the attentional avoidance.

Significant results for facilitated attention among anxious individuals were found in studies (e.g. Fox, Russo, Bowles, & Dutton, 2001; Yiyend & Mathews, 2001). Data suggest that facilitated attention towards threat is moderated by the threat intensity and its duration during task performance (i.e. highly threatening and presented 100 ms or less). Studies have therefore demonstrated that selective attention detects faster threat cues than unrelated stimuli (Williams, Watts, MacLeod, & Mathews, 1997). The second element of attentional bias concerned the attentional disengagement. In anxiety disorders, it appears that the disengagement component is not performed accurately. Studies evidenced a significant difficulty to disengage selective attention towards threat cues (automatic biases for threatening information advanced and inhibition deficit) (Amir, Elias, Klumpp,
Przeworski, 2003; Eysenck et al., 2007) leading to increased emotional reactivity. The maladaptive attentional disengagement is considered as the core factor of preservation of the anxiety state.

Lastly, cognitive-motivational designs (e.g. Mogg & Bradley, 1998) demonstrated that hypervigilance and avoidance co-occur in a temporally ordered manner in anxiety disorders. Anxious individuals initially direct their attention towards threat (facilitated attention deployment for threat-cueing stimulus) but afterwards, avoid detailed processing of such stimulus in an attempt to decrease their anxious state. In other words, anxious individuals are preoccupied to vigilantly scan the environment for threats (Williams et al., 1997).

2.2.1.2. Memory. The second category involves the memory and especially the episodic and the autobiographical memory. It has been proposed that one factor that may contribute to the maintenance of negative beliefs and avoidance behaviour is the dysfunctional retrieval of past mental events from autobiographical and episodic memory (Mathews & MacLeod, 2005; Mitte, 2008). Researchers proposed that clinical anxious individuals tend to explicitly re-experienced past fear experiences (episodic memory process) when confronted with aversive stimulus, which in turn, potential fear responses. Moreover, studies observed impaired episodic memory for neutral, emotionally irrelevant information (de Quervain & Margraf, 2008).

2.2.2. Hot cognition deficits in anxiety disorders

Cognition could be defined as all mental processes and skills in which individuals engage on a daily basis (e.g. memory, problem solving, decision-making). The cognition allows generating new knowledge through mental processes and helping to use the acquired knowledge in a certain situation. The metacognition is usually conceptualized as “thinking about thinking”. Metacognition refers to beliefs and appraisals held about cognition. Metacognition is made up of two components: knowledge and regulation (Friedenberg & Silverman, 2006).

Metacognition of knowledge includes explicit beliefs (declarative/verbally expressed) (e.g. worrying can cause distress) and implicit beliefs (procedural/not directly verbally penetrable) (e.g. use of heuristics in forming social judgements) (Robinson, Vytal, Cornwell, & Grillon, 2013).

These metacognitive beliefs could be positive (i.e. advantages of engaging in cognitive activities) or negative (i.e. beliefs concerning the meaning and dangerousness of thoughts and cognitive experiences) (Wells, 2007). Conversely, metacognition of regulation is the monitoring of one’s cognition including planning activities, awareness of comprehension and evaluation of the efficacy of monitoring processes and strategies. Metacognition is then conceptualized as a dynamic and multi-level information processing (Wells, 2000).

2.2.2.1. Content of cognitions in anxiety disorders. In anxiety disorders, combined maladaptive knowledge, experiences and strategies gave rise to a toxic pattern of thinking that lead to psychological vulnerability and disturbance (e.g. fear of negative evaluation, negative evaluation of positive event, and overestimation of threat, rumination but also inflated responsibility) (Cisler & Koster, 2010; Robinson et al., 2013).

2.2.2.2. Metacognition in anxiety disorders. In anxiety disorders, the central roles of worry and IU as general factors contributing to emotional disorders have been highlighted. According to researchers, certain types of metacognition (especially metacognitive knowledge/positive and negative beliefs) are impaired in anxiety disorders (Wells, 2007).

The influential “Self-Regulatory Executive Function Model” (S-REF; Figure 1) is widely used to understand the development and maintenance of anxiety disorder across a cognitive psychopathology perspective. The S-REF model (S-REF; Wells & Matthews, 1994) is based upon a multi-level architecture integrating three interacting cognitive levels: (1) the level of automatic and reflexive-driven processing (the “on-line” level), (2) the level of voluntary (controlled processing demanding
attentional resources) and (3) the level of stored self-beliefs and strategies for self-regulation stored in long-term memory.

The first automatic and reflexive level comprises stimulus-driven information, which is proceeded outside of the conscious mental state. However, stimulus-driven information may pervade into consciousness, which induces adverse negative automatic thoughts (or intrusions) and activates the S-REF (the middle level).

The second level of the model includes a voluntary and a conscious appraisal of events (i.e. control of action and thought). The execution of on-line level of processing requires attentional resources, which by nature are restricted.
The third level involves self-beliefs and strategies for regulation stored in the long-term memory. Two types of self-beliefs are described: (1) declarative and (2) procedural self-beliefs. Declarative self-beliefs consist of explicit statements (self-knowledge about the meaning of thoughts) such as: “I am a worrier”. Conversely, procedural self-beliefs are plans that guide the execution of the controlled processes and have a metacognitive status. Two modes (processing configurations) can be executed and are involved in modifying beliefs: (1) object mode and (2) metacognitive mode.

When in object mode, thoughts (i.e. appraisals) and perceptions are taken as unevaluated and accurate representations of events; this is the default mode of cognitive operation that usually runs in daily circumstances. When in metacognitive mode, the individual is distanced from thoughts, and thoughts and perceptions can be evaluated and not necessarily accepted as direct representations of reality. (Wells, 2000, p. 16)

The S-REF model hypothesizes that in the case of emotional disturbances, this metacognitive system becomes dysfunctional, resulting in a toxic pattern: the “Cognitive Attentional Syndrome” (CAS). This toxic pattern is characterized by recurrent styles of thinking in response to negative thoughts (worry and rumination), intensified self-focused attention to threat, decreased cognitive functioning, activated dysfunctional self-beliefs and increased maladaptive coping strategies.

Lastly, the metacognitive model (Wells & Matthews, 1994) argues that the psychological disturbance is maintained by a combination of perseverative thinking styles, maladaptive attentional routines (sustained attention to threatening cued-stimuli) and dysfunctional behaviours (coping strategies) that constitutes the CAS (Wells, 2000).

3. Method

3.1. Search strategy for identification studies

It is noteworthy that none ethical approval for this type of study is needed.

Sources in the current review have been drawn from several databases: Scopus, PubMed and PsycArticles. The following inclusion criteria were established: (1) year of publication: studies published between 1 January 2005 and 1 January 2015; (2) language: only English publications; (3) method: quantitative and qualitative experimental studies (cross-sectional, longitudinal, randomized controlled study); (4) article design: only peer-reviewed articles and (5) target population: clinical adult sample.

Please note that the search procedure was done on a range of 10 years (studies led between 2005 and 2015). This choice is argued by the fact that the IU is a relatively recent concept (early 2000s).

There were restrictions (exclusion criteria) according to: (1) type of source: book chapters, guidelines, commentaries and dissertations and (2) target population: children, adolescents, students and the elderly and non-clinical sample.

It is noteworthy that studies about children, adolescents or elderly were not taken into account because most of the literature considers these issues and would require an additional clinical review. So excluded studies did not focus on the intolerance of uncertainty (IU) assessed in a clinical adult sample.

3.2. Algorithmic procedures

Figure 2 shows the Prisma diagram of trial identification and selection. An initial algorithm (Algorithm A = intolerance of uncertainty + anxiety disorders) was encoded through databases. Three hundred and thirty-two results listed by date (2005–2015) were obtained.
Figure 2. Algorithmic diagram of study identification and selection.
The following process was to pigeonhole the relevant studies within the research cluster. These were identified as following: anxiety disorders perspective (cluster A) and cognitive processes perspective (cluster B).

Fifty studies involved anxiety disorders studies (cluster A) of which eighteen investigated the GAD (36%), nine concerned the OCD (18%), fourteen gathered mixed clinical studies (28%), five were about anxiety studies (10%), three related to the panic disorder (PD) (6%) and one was a qualitative study (2%).

Studies not deemed eligible had no decisive criteria (heterogeneous studies (49.07%). Through these heterogeneous studies, 48.68% included clinical off topic themes (e.g. psychosis, spinal injury, breast cancer, Meniere’s syndrome), 31.68% were already found through databases (redundant data), 24.03% incorporated non-eligible population (e.g. child, adolescent), 13.9% of the studies were therapeutic researches, 9.55% included psychometric tools validation and 3.84% concerned the study design (i.e. review of the literature or meta-analysis).

3.3. Refinement data extraction
Further algorithms were encoded through databases in order to highlight the cognitive processes (and its components) implied in the IU. A second algorithm was encoded: Algorithm B = intolerance of uncertainty + cognition and a third algorithm was encoded: Algorithm B’ = intolerance of uncertainty + cognitive process. This second step of refinement data extraction enabled the addition of twenty-six new results of which were redundant data (K = 10), were off topic (K = 12) and four were integrated into the cluster B (cognitive processes).

It is noteworthy that analogies were also considered such as uncertainty (concern, scepticism, unpredictability, doubtfulness, hesitancy and wonder), anxiety disorders (apprehension, doubt, psychopathology, panic, depression, GAD, distress, restlessness), cognition (perception, awareness, insight, evaluation) and cognitive process (attention, biases, memory, controlled, mental). Several spreadsheets were created in order to organize the relevant data. Two tables are included in the appendices section.

4. Results

4.1. Cluster A: IU and anxiety disorders perspective

4.1.1. Core clinical issues in GAD
Generalized Anxiety Disorder [DSM V code: 300.02; American Psychiatric Association, 2013] is characterized by excessive anxiety and worry, occurring more days than not for at least 6 months, about various activities or events. The focus of the anxiety and the worry is not confined to features of Axis I disorders (e.g. linked for instance of a panic attack) and it is difficult for the individual to control the worry. The anxiety, the worry or somatic disturbance cause clinically significant distress or, impairment in social or other areas of functioning. Lastly, the disturbance is not due to substance abuse (American Psychiatric Association, 2013).

Eighteen studies have investigated the GAD issue according to the IU since the early 2005s. Seventeen studies used cross-sectional design and one was a case study. The gathering procedure of results was led according to overriding models established on GAD: the Emotion Dysregulation Model (EDM; Mennin, Heimberg, Turk, & Fresco, 2005) (1), the Avoidance Model of Worry (AMW; Borkovec, Alcaine, & Behar, 2004) (2) and the Intolerance of Uncertainty Model (IUM; Dugas, Gagnon, Ladouceur, & Freeston, 1998) (3). These models can be classified into three fields: cognitive models (i.e. IUM), emotional/behavioural (i.e. EDM) and an integrated field (i.e. AMW).

The EDM demonstrated that individual with GAD experience emotional hyperarousal, poor understanding of emotions, negative cognitive reactions to emotions and maladaptive emotion
management and regulation. Studies postulating an emotion dysregulation in GAD observed that the combination of the emotional hyperarousal with a poor understanding of emotions leads to the perception that emotions are threatening. These results stipulate that GAD patients become overwhelmed, anxious, or uncomfortable when emotions occur, thereby creating a toxic feedback loop (e.g. Andreescu et al., 2011; Palm, Elliott, McKie, Deakin, & Anderson, 2011). Other results have demonstrated the extreme hypervigilance for threatening information and increased selective attention either towards or away from emotions, relevant negative beliefs (Nitschke et al., 2009) and impulsivity (Whalen et al., 2008).

Other studies using the EDM suggested that emotion dysregulation is the core predictor to GAD diagnosis. Indeed, individual with GAD have emotional reactions that occur more easily and intensely than non-anxious people and they have significant difficulties in their ability to identify and clarify their emotional experience (Andreescu et al., 2011). Further, GAD patients also display negative cognitive control, as demonstrated a greater endorsement of catastrophic beliefs concerning the issue of emotions (comprising positive emotions) (Greenberg, Carlson, Cha, Hajcak, & Mujica-Parodi, 2013). The ability to soothe one’s self when experiencing negative emotions was observed to be distorted in GAD compared to non-anxious (Palm et al., 2011).

Lastly, some neural underpinnings in emotion dysregulation in GAD patients have been advanced. The most impressive findings have focused on the role of brain deficits into the anterior cingulate and dorsal medial prefrontal cortex (Paulesu et al., 2010). Other studies (e.g. Whalen et al., 2008) have observed activation during uncertainty and ambiguous situation of the dorsal anterior cingulate cortex (dACC), the rostral anterior cingulate cortex (rACC) and the amygdala. Results suggest the dACC detects conflict, while the rACC evaluates emotional information and is potentially involved in emotion regulation. Moreover, some studies have observed hyperactivity in the dACC, the amygdala and the insula cortex and hypo activation of the rACC (e.g. Hölzel et al., 2013).

The AMW postulated the central function of worry in the development and the maintenance of GAD. The forerunners of the AMW defined the worry as “chain of thoughts and images, negatively affect-laden and relatively uncontrollable” (Borkovec, Robinson, Pruzinsky, & DePree, 1983, p. 10). The AMW advocates that worry emphasizes the commitment in the field of catastrophizing (i.e. a succession of “what if” questions to each thought generated), which in turn results in an increased discomfort, an emotional distress and hyperarousal.

Other studies evidenced that worry is seen as a positive coping factor in GAD. Worry is reinforced by positive beliefs about worrying (i.e. worry is helpful for problem-solving, motivating but also avoiding future negative topics) (Dugas et al., 2007; Robichaud, 2013). Conversely, some studies evidenced that the function of worry is a cognitive avoidance response to perceiving future threats (Crittendon & Hopko, 2006; Lee, Orsillo, Roemer, & Allen, 2010). Moreover, two types of avoidant functions posited for worry are proposed: (1) worry is a cognitive attempt to generate cognitive patterns to anticipate threatening topics and (2) worry is a verbal-linguistic thought that inhibit mental imagery and associated with somatic and emotion arousal (Khawaja, McMahon, & Strodl, 2011; Ruggiero et al., 2012).

Finally, studies based on IUM argued the dynamic process between the IU and GAD. Four factors distinguish GAD patients from healthy individuals: (1) to be intolerant of uncertainty, (2) to have positive beliefs about worry, (3) to use cognitive avoidance and (4) to present negative problem orientation.

Results retrieved from algorithmic procedure demonstrated that GAD patients do not tolerate uncertain or ambiguous situations, interpret them as potential threats and worry would serve to either help them to cope or to prevent those events from occurring at all (i.e. positive beliefs about
worry) (Boelen & Reijntjes, 2009; Koerner & Dugas, 2008). Results suggested that misinterpretation of events leads to (1) negative problem orientation, (2) cognitive avoidance (e.g. thought suppression or replacement), both of which allow exacerbating the worry and the anxiety (van der Heiden et al., 2010).

Lastly, IUM posits that IU is the core transdiagnostic factor across anxiety disorders such as anxiety, OCD or panic disorder (PD) (van der Heiden et al., 2010).

In a nutshell, results found through databases emphasize the importance of the avoidance process of emotional events in IU. The AMW observes that worry is seen as a strategy for avoiding emotional stimuli (e.g. vivid images) whereas the IUM asserts worry as a toxic strategy for avoiding uncertainty and the EDM identifies worry as an ineffective coping strategy to regulate internal emotions.

4.1.2. Core clinical issues in OCD

The Obsessive–Compulsive Disorder (DSM V code: 300.3; American Psychiatric Association, 2013) is characterized by the presence of obsessions (i.e. obsessive preoccupations) and compulsions (i.e. repetitive behaviours) or both. Obsessions and compulsions are very time-consuming (i.e. take more than 1 h per day) and cause clinically distress or impairment in social, occupational or other areas of functioning. The obsessive-compulsive symptom are not due to substance or chemical abuse (e.g. drug or a medication) and is not better explained by the symptoms of another mental disorder (e.g. excessive worries in GAD, body dysmorphic disorder, hoarding disorder, trichotillomania [hair-pulling disorder], excoriation disorder [skin-picking] or ritualized eating behaviour) (American Psychiatric Association, 2013).

Nine results have studied the OCD issue according to the IU since the early 2005s. Eight of these nine studies are quantitative studies and one was a qualitative study (Kobori, Salkovskis, Read, Lounes, & Wong, 2012). Quantitative results showed that patients with OCD, present more intrusive thoughts (Kaiser, Bouvard, & Milliery, 2010), produce high negative affects (Taylor, McKay, & Abramowitz, 2005) and perceive as difficult to control (Taylor et al., 2005; Williams & Grisham, 2013). Studies also revealed the significant link between IU and perfectionism in this clinical population (Calleo, Hart, Björgvinsson, & Stanley, 2010). Consistent results of the link between worry and obsession were found. Beliefs in perfectionism were similarly increased in clinical OCD patients (e.g. Belloch et al., 2010; Calamari et al., 2006).

Certain cognitive impairment was found through databases outcomes. Impaired performance on the Object Alternation Task was observed. Indeed, OCD patients committed more perseveration errors following prior correct response from controls (Williams & Grisham, 2013). Studies evinced also an attentional bias towards threatening words but also a significant cognitive inhibition deficit (Calamari et al., 2006).

Lastly, qualitative study (Kobori et al., 2012) highlighted four main themes in terms of reassurance seeking: (1) interpersonal concern and worry, (2) revulsion to seek reassurance, (3) difficulties to understand the uncertainty and its normal state (difficult position to make sense) and (4) extreme effort of vigilance. All of these themes maintain in the long run the worry and the IU (vicious circle).

4.1.3. Others core clinical issues

This section of results highlights “heterogeneous studies” which either combined anxious disorders in accordance with the processes in the IU or isolated psychopathological disorders. Twenty three studies among which 14 were mixed studies (combined psychological pathologies), 5 were studies led among clinical anxious population and 3 investigated the PD and one was a qualitative study.
As regards combined psychopathological studies, IU has been observed to be higher in the clinical sample than in controls (Agheli, Hasanzadeh, & Ghasemian, 2013; Jacoby, Abramowitz, Buck, & Fabricant, 2014; Nelson, Shankman, & Proudfit, 2014).

McEvoy and Mahoney (2012) found that IU explained unique variance in all symptoms after controlling for neuroticism and major depressive disorder. Results showed that neuroticism was highly correlated with IU ($r = .55$) and interestingly extraversion was negatively correlated with IU ($r = .18$).

As regards social anxiety disorders (Carleton, Fetzner, Hackl, & McEvoy, 2013; Carleton et al., 2014), analysis of variance revealed one statistically significant difference in IU Scale-12 scores across diagnostic groups in the clinical sample ($p < .01$; $\eta^2 = .03$) than people with PD (Carleton et al., 2012).

Study led on eating disorders highlighted that the IU score appears to be higher than controls with more distress (García-Soriano, Roncero, Perpiñá, & Belloch, 2014). The qualitative study (Sternheim, Konstantellou, Startup, & Schmidt, 2011) demonstrated that patients with anorexia nervosa perceive uncertainty as a stressor and use more avoidance strategies.

Concerning, clinical anxious group present more intrusive thoughts (Gutierrez, Hershey, & Douglas, 2013; Mahoney & McEvoy, 2011), worry, cognitive avoidance (Dupuy & Ladouceur, 2008) and distress (Jacoby et al., 2014) compared to controls.

Lastly, neurological studies evinced that IU was associated with reduced frontal EEG asymmetry (Nelson et al., 2014) but also evidence of emotion-related disorder-specificity emerged in medial prefrontal cortex and amygdala (Blair et al., 2012).

Evidence that IU does not share the unique link with GAD pattern raises the question of its status. Studies propose that IU is a broad transdiagnostic maintaining risk factor but also IU is always found in disorders characterized by negative affects. Past studies have found already this link (e.g. Dugas, Gosselin, & Ladouceur, 2001).

Outcomes retrieved from databases revealed the potential role of IU as a correlate of emotional disorders and allow also to understand in which way it may play a role on cognitive mechanisms or processes by which it is related to these disorders (Table 1). This question would be investigated in the next section (Cluster B).

4.2. Cluster B: IU and cognitive perspective

4.2.1. IU and worry

Research on worry has burgeoned since the early 1990s. The worry is observed at first as an adaptive factor but can become pathological if it is excessive at the individual’s. The present section investigates the link between excessive worries and IU. Worry is considered as an effort to problem-solve in an uncertain situation, where ultimate issues may be aversive. In line with this definition, Mathews (1990) conceptualized worry as “thwarted” attempts to problem-solve, during danger, which is constantly rehearsed, but no issues found. This evidence suggested that pathological worriers (individuals with excessive and uncontrollable worries) have a lower threshold for uncertainty and ambiguous situations.

Ten studies have examined the relationship between worry and IU independently of anxiety disorders. Worry is observed to be a process allowing the avoidance of vivid images and intense negative emotions in the short-run (Zlomke & Jeter, 2014). Consequently, the worry is likely to prevent access to fear structures in memory and allows inhibition of negative emotional stimuli (Buhr & Dugas, 2009; Dash & Davey, 2012). Indeed, IU triggers worry as a result of experiencing uncertainty (IU is a filter through which individuals scan their environment). IU seems to share the unique
Table 1. Summary of included studies on clinical comorbidities related to IU, in chronological order

<table>
<thead>
<tr>
<th>ID study</th>
<th>Design of study</th>
<th>Syndrome</th>
<th>Sample (N)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalized anxiety disorders (GAD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Emotion dysregulation hypothesis (EDM)</td>
<td></td>
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<tr>
<td>Greenberg et al. (2013)</td>
<td>CR</td>
<td>GAD</td>
<td>32 GAD</td>
<td>There is a link between deficits in fear regulation and the prevalence of GAD</td>
</tr>
<tr>
<td>Hölzel et al. (2013)</td>
<td>CR</td>
<td>GAD</td>
<td>26 GAD</td>
<td>Higher amygdala activation is observed in GAD with emotion dysregulation</td>
</tr>
<tr>
<td>Andreescu et al. (2011)</td>
<td>CR</td>
<td>GAD</td>
<td>7 GAD (elderly patients)</td>
<td>GAD patients tend to use not effective thoughts strategies namely though suppression that is involved in the maintenance of worries</td>
</tr>
<tr>
<td>Palm et al. (2011)</td>
<td>CR</td>
<td>GAD</td>
<td>15 GAD</td>
<td>There is a link between the hypo-responsivity to external emotional stimuli and GAD</td>
</tr>
<tr>
<td>Paulesu et al. (2010)</td>
<td>CR</td>
<td>GAD</td>
<td>8 GAD</td>
<td>Deficits in anterior cingulate and dorsal medial prefrontal cortex were found in GAD patients with severe emotion dysregulation</td>
</tr>
<tr>
<td>Nitschke et al. (2009)</td>
<td>CR</td>
<td>GAD</td>
<td>14 GAD</td>
<td>GAD patients showed more anticipatory activity (emotion dysregulation) than controls in the bilateral dorsal amygdala preceding aversive and neutral pictures</td>
</tr>
<tr>
<td>Whalen et al. (2008)</td>
<td>CR</td>
<td>GAD</td>
<td>15 GAD</td>
<td>GAD patients showed more reactivity in the Rostral Anterior Cingulate Cortex (ACC) and hypovigilant in the amygdala. Emotion dysregulation is observed in GAD patients</td>
</tr>
<tr>
<td><strong>The avoidance of Worry Hypothesis (AMW)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robichaud (2013)</td>
<td>Case study</td>
<td>GAD</td>
<td>1 (clinical case)</td>
<td>IU and its components (positive beliefs about the usefulness of worry, negative problem orientation and cognitive avoidance) are intractably linked to GAD</td>
</tr>
<tr>
<td>Ruggiero et al. (2012)</td>
<td>CR</td>
<td>GAD</td>
<td>118 GAD</td>
<td>Deficits in metacognition and control beliefs in the cognitive process reinforced the development of worry</td>
</tr>
<tr>
<td>Lee et al. (2010)</td>
<td>CR</td>
<td>GAD</td>
<td>50 GAD</td>
<td>GAD patients experiment more experiential avoidance, distress and angry compared with control group</td>
</tr>
<tr>
<td>Dugas et al. (2007)</td>
<td>CR</td>
<td>GAD</td>
<td>84 GAD</td>
<td>GAD severity depends on the magnitude of positive beliefs about worry but also the development of maladjusted cognitive avoidance strategies. Intolerance of uncertainty and the negative problem orientation have a significant link with GAD prevalence</td>
</tr>
<tr>
<td>Pawluk and Koerner (2013)</td>
<td>CR</td>
<td>GAD</td>
<td>63 GAD</td>
<td>Negative affects and lower functional impulsivity were predictors of GAD severity</td>
</tr>
<tr>
<td>Khawaja et al. (2011)</td>
<td>CR</td>
<td>GAD</td>
<td>107 GAD</td>
<td>The levels of IU are implied in the severity of GAD. Moreover, meta-worry (positive beliefs about the usefulness of worry) distinguishes these three groups (more meta-worry in the high GAD group compared to middle or low GAD group)</td>
</tr>
<tr>
<td>Crittendon and Hopko (2006) (Study 1)</td>
<td>CR</td>
<td>GAD</td>
<td>115 sample of older 183 young adults</td>
<td>GAD patients tend to have more worries but also suffer from more distress and anxiety than controls</td>
</tr>
<tr>
<td><strong>The intolerance of uncertainty hypothesis (IUM)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van der Heiden et al. (2010)</td>
<td>CR</td>
<td>GAD</td>
<td>137 GAD</td>
<td>Neuroticism and symptoms of GAD were mediated by the factors of IU and negative metacognitions</td>
</tr>
<tr>
<td>Boelen and Reijntjes (2009)</td>
<td>CR</td>
<td>GAD</td>
<td>126 GAD</td>
<td>IU is linked to symptom levels of GAD, OCD and social anxiety, but not depression, when controlling the shared variance among these symptoms</td>
</tr>
</tbody>
</table>

(Continued)
Table 1. (Continued)

<table>
<thead>
<tr>
<th>ID study</th>
<th>Design of study</th>
<th>Syndrome</th>
<th>Sample (N)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koerner and Dugas (2008)</td>
<td>CR</td>
<td>GAD</td>
<td>199 GAD (110 low in IU and 89 high in IU)</td>
<td>Individuals who are intolerant of uncertainty (high scores) appraised all situations (neutral or ambiguous) as more threatening. Results showed that ambiguous situations partly mediate the relationship of IU to worry.</td>
</tr>
<tr>
<td>González, Ibáñez and Cubas (2008)</td>
<td>CR</td>
<td>GAD</td>
<td>503 GAD</td>
<td>GAD patients tend to be more intolerant of uncertainty but also use more belief suppression strategies</td>
</tr>
</tbody>
</table>

**Obsessive-compulsive disorders**

| Jacoby, Fabricant, Leonard, Riemann and Abramowitz (2013) | CR              | OCD      | 205 OCD    | Inhibitory intolerance of uncertainty (unacceptable thoughts of worry) is linked with obsessive-compulsive symptoms. Patients with compulsions and obsessions tend to use more mental neutralizing strategies (e.g. suppression and avoidance) |
| Williams and Grisham (2013) | CR              | OCD      | 89 OCD    | OCD patients tend to present anxiety and more non-adaptive physiological responses |
| Kobori et al. (2012) | QL              | OCD      | 10 OCD    | Four main themes in terms of reassurance seeking: (1) interpersonal concern and worry, (2) revulsion to seek reassurance, (3) difficulties to understand the uncertainty and its normal state (difficult position to make sense) and (4) extreme effort of vigilance |
| Belloch et al. (2010) | CR              | OCD      | Study 1: 573 non-clinical subjects | Study 1/Study 2: OCD patients use dysfunctional beliefs (e.g. negative thoughts overestimated, cognitive control, overestimation of threat, intolerance of uncertainty, perfectionism) |
| Calleo et al. (2010) |                | OCD      | 70 OCD    | Perfectionism and intolerance of uncertainty are linked with worry. Beliefs and cognitive control of thoughts and thought-action fusion are linked with obsession severity |
| Kaiser et al. (2010) | CR              | OCD      | 96 OCD    | Washers, rumimators and checkers tend to present more impaired thought control strategies than controls |
| Radomsky, Ashbaugh and Gelfand (2007) | CR              | OCD      | 33 OCD    | Checkers have greater trait anger than controls. Moreover, beliefs about perfectionism and intolerance of uncertainty are positively correlated with trait anger |
| Calamori et al. (2006) | CR              | OCD      | 367 OCD   | Both OCD groups (low and high obsessive beliefs) present an overestimating of threat, perfectionism thoughts and are intolerant of uncertainty |
| Taylor et al. (2005) | CR              | OCD      | 202 OCD   | Hierarchical results showed 3 core factors/processes in OCD: (i) responsibility and overestimation of threat, (ii) perfectionism and intolerance of uncertainty and (iii) importance and control of thoughts |

**Mixed studies (Combined psychopathological disorders as regards IU)**

| Laposa, Collimore, Hawley and Rector (2015) | CR          | OCD + ANX | Not reported | OCD and anxious patients tend to present more distress of tolerance. Moreover distress of tolerance predicted not the severity of OCD |
| Garcia-Soriano et al. (2014) | CR          | OCD + ED  | 79 OCD      | In the OCD group, intolerance of uncertainty and thought importance predicted emotional distress |
| Nelson et al. (2014) | CR          | MDD + PD  | 156 MDD (+PD) + HC | Experimental group (MDD+PD) present high scores for intolerance of uncertainty compared to control group. IU is seen as a mediator between MDD and reduced reward anticipation |
| Agheli et al. (2013) | CR          | GAD + OCD | 50 GAD      | GAD and OCD patients reported greater intolerance of uncertainty than controls |
|                               |              |           | 50 OCD      |                             |
|                               |              |           | Controls    |                             |

(Continued)
<table>
<thead>
<tr>
<th>ID study</th>
<th>Design of study</th>
<th>Syndrome</th>
<th>Sample (N)</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manber Ball, Ramsawh, CampbellSills, Paulus and Stein (2013)</td>
<td>CR</td>
<td>GAD + PD + HC</td>
<td>28 GAD patients</td>
<td>GAD and PD patients showed less dorsolateral and dorsomedial prefrontal cortex activation than controls. It is mentioned that these areas are implied in emotion regulation and are impaired in GAD and PD</td>
</tr>
<tr>
<td>Boswell, Thompson-Hollands, Farchione and Barlow (2013)</td>
<td>L</td>
<td>MDD + ANX</td>
<td>Not reported</td>
<td>Intolerance of uncertainty is positively correlated with depressive symptoms and the severity of worry</td>
</tr>
<tr>
<td>Anderson et al. (2012)</td>
<td>CR</td>
<td>GAD + ANX</td>
<td>GAD group and anxious group</td>
<td>Results observed no differences between GAD and anxious patients in their interpretations of negative or positive appraisals</td>
</tr>
<tr>
<td>Blair et al. (2012)</td>
<td>CR</td>
<td>GAD + SAD</td>
<td>34 GAD</td>
<td>Experimental group (GAD + SAD) reported hypoactivity in the medial prefrontal cortex and amygdala compared to controls. Moreover, these areas are implied in emotion regulation. Evidence of emotion regulation impairments is advanced in GAD or SAD</td>
</tr>
<tr>
<td>Carleton et al. (2012)</td>
<td>CR</td>
<td>ANX + GAD + OCD + MDD</td>
<td>376 clinical sample</td>
<td>Intolerance of uncertainty is seen as a transdiagnostic factor across anxiety disorders provoking distress and leading to the preservation of symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>428 HC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>571 community sample</td>
<td></td>
</tr>
<tr>
<td>Mahoney and McEvoy (2012)</td>
<td>CR</td>
<td>ANX + MDD</td>
<td>218 comorbid sample</td>
<td>Intolerance of uncertainty is a maintaining factor for anxious and depressed patients. The degree of comorbidity plays a pivotal role in the prediction of prospective IU</td>
</tr>
<tr>
<td>McEvoy and Mahoney (2012)</td>
<td>CR</td>
<td>ANX + MDD</td>
<td>328 comorbid sample</td>
<td>Intolerance of uncertainty is linked with neuroticism, SAD, PD, OCD, GAD and MDD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Results reported that intolerance of uncertainty was a significant partial mediator between neuroticism and all symptom measures</td>
</tr>
<tr>
<td>Yook, Kim, Suh and Lee (2010)</td>
<td>CR</td>
<td>GAD + MDD</td>
<td>28 GAD</td>
<td>Worry, rumination, intolerance of uncertainty, anxiety and depressive symptoms correlated significantly with each other. Worry partially mediated the relationship between intolerance of uncertainty and anxiety whereas rumination completely mediated the relationship between intolerance of uncertainty and depressive symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>27 MDD</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 GAD/MDD</td>
<td></td>
</tr>
<tr>
<td>Blair et al. (2008)</td>
<td>CR</td>
<td>GAD</td>
<td>17 GAD + 17 SAD</td>
<td>17HC</td>
</tr>
<tr>
<td>Dupuy and Ladoouceur (2008)</td>
<td>CR</td>
<td>GAD + MDD</td>
<td>32 GAD /MDD</td>
<td></td>
</tr>
</tbody>
</table>

### Anxiety disorders

| Jacoby et al. (2014) | CR | ANX | 69 ANX | During the Beads Task, anxious participants reported greater distress than controls |
| | | | 26 HC | Intolerance of uncertainty is positively correlated with draws to decision and distress during the task |
| Bertrams, Englert, Dickhäuser and Baumeister (2013) | CR | ANX | Study 1: 67 ANX | In study 1 and study 2: the state of anxiety is negatively correlated with performance of verbal learning. In study 3: worry is linked with cognitive distraction strategies |
| | | | Study 2: 96 ANX | |
| | | | Study 3: 99 ANX | |
| Gutierrez et al. (2013) | CR | ANX | 87 ANX (related to retirement anxiety) | Participants with retirement anxiety experienced impairments in information processing that ensue from the negative emotional content linked to retirement concepts in long-term memory |
relationship with worry gathering cognitive avoidance, metaworry and negative problem orientation (Fergus & Wu, 2013; Kertz, Stevens, McHugh, & Björgvinsson, 2015).

In addition, some studies have observed that worriers who are intolerant of uncertainty tend to perceive ambiguous situations as a threat and interpret the situation more negatively (i.e. catastrophizing scenario) than control group (e.g. Davey, Eldridge, Drost, & MacDonald, 2007). As already mentioned, the worry is significantly linked to IU. In the face of uncertainty, individuals who are high in IU seem to be more prone to worry. Studies concluded to the central role of IU in the development and the maintenance of worry itself. IU leads to “What if” thinking that in turns lead to more excessive and uncontrollable worry (i.e. IU is seen as the most salient predictor of worry) (Ottaviani et al., 2014; Zlomke & Jeter, 2014).

In a nutshell, individuals who are high in IU present more positive beliefs about worry (e.g. Davey et al., 2007), tend to a negative problem orientation (Zlomke & Jeter, 2014) and use more cognitive avoidance (e.g. Kertz et al., 2015).

### 4.2.2. IU and response to uncertain threat aversion

Individual is bombarded with uncertainty and potential threats throughout their everyday life (e.g. personal uncertainty, perceptual surprises or cognitive goal conflicts). These aversive situations amplify negative impacts of event and motivate individuals to resolve them.

The resolution of uncertainty occurs through the identification by the individual of the relationship between environmental cues and subsequent outcomes of the situation (Britton & Davey, 2014).

Cognitive paradigms have shown the link between certain types of cognition and emotions. For instance, negative beliefs about personal skills (e.g. “I am a loser”) lead to depression. As also
mentioned in section A (IU and Anxiety disorders) a large body of literature indicates that anxiety disorders are associated with negative beliefs or perceptions, automatic thoughts concerning threatening stimuli and the inability to resolve them (e.g. Cisler & Koster, 2010).

Since the early 2005s until today, we retrieved six studies investigating IU related to the threat construct. All of these studies advanced an overestimation of threat stimulus when intolerant of uncertainty individual is confronted with an ambiguous situation (e.g. Grupe & Nitschke, 2011; Nelson & Shankman, 2011). Indeed, individual with high IU associated the ambiguity with a higher occurring probability of negative events (Dugas et al., 2005).

Moreover, cognitive studies have already mentioned the intrinsic link between selective attention and threat cues (e.g. Amir et al., 2003). Studies demonstrated that this sensitivity to threat impaired its management (Britton & Davey, 2014), the efficiency of decision-making (Luhmann, Ishida, & Hajcak, 2011), the cognitive control of threat (Nelson & Shankman, 2011) and created information processing biases (Dugas et al., 2005) (Table 2).

5. Discussion
The current review aimed to probe the relations between IU and the anxiety disorders and its cognitive components. The first step concerns the estimation of IU with GAD and OCD and its clinical aspects. The algorithmic procedure has allowed the retrieving of fifty empirical studies of 66 studies (covering approximately 75% of the results for the review). IU is observed to share a unique relationship with anxiety disorders (namely GAD, OCD, MDD) and is seen as a predictor (transdiagnostic risk factor).

Researchers emphasized significant perception of threat and more reactions of hypervigilance when anxiety is combined with IU. Certain neural dysfunctions are advanced namely the insula cortex, dACC and the amygdala when IU individuals are confronted with ambiguous stimuli.

Paradigms in anxiety disorders have already demonstrated impairments in hot and cold cognition. As regards cold cognition studies evidenced impairments in attentional and memory processes. Anxious individuals seem to have a facilitated attentional deployment, a difficulty to disengage allocated resources on specific stimuli (especially threatening stimuli) and they used more easily an attentional avoidance. The memory process has revealed a cognitive dysfunction in the episodic and the autobiographical memory (impairments in retrieval process). Concerning the hot cognition studies demonstrated several dysregulation of thought and maladaptive knowledge in anxiety disorders given rise to a defective pattern of thinking and leading to diverse psychological vulnerabilities (e.g. poor orientation problem, avoidance, metaworry).

Studies investigating GAD and IU demonstrated the central role of IU in the development and the maintenance of symptoms (high rate of comorbidity). Other features have been advanced such as positive beliefs about worry moderating negatively the outcome, a poor problem orientation (i.e. impairments in problem perception, problem attribution, problem appraisal and personal control of these beliefs), and cognitive avoidance of threatening mental images (i.e. semantic cognitive activity has the effect of decreasing somatic activity resulting from vivid or fearful imagery).

Researchers studied OCD and IU evidenced intrusive thoughts producing emotional dysregulation and impairments in cognitive control. It has been advanced that rituals and compulsions serve to decrease the distress resulting from uncertainty about a potential threat stimulus. These results have been also observed in other clinical populations (e.g. depression). All of these studies have highlighted the central mechanism of negative repetitive thoughts (i.e. worry) through GAD, OCD and MDD. It has been advanced that worry mediates the relationship of IU to symptoms of these psychopathological disorders when the IU is seen as the predictor.
### Table 2. Summary of included studies on cognitive processes related to IU, in chronological order

**Cognitive hypothesis**

<table>
<thead>
<tr>
<th>ID study</th>
<th>Design of study</th>
<th>Syndrome</th>
<th>N</th>
<th>Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>A/Worrying process</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Byrne, Hunt and Chang (2015)</td>
<td>CR</td>
<td>IU</td>
<td>N = 104</td>
<td>Ambiguity and unpredictability are core components in IU that stem from different types of responses</td>
</tr>
<tr>
<td>Kertz et al. (2015)</td>
<td>CR</td>
<td>IU</td>
<td>N1 (XP) = 281</td>
<td>Worry is linked with high levels of IU, cognitive avoidance, negative beliefs of worry (metaworry) and negative problem orientation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2 (HC) = 123</td>
<td>In the experimental group (XP), negative problem orientation and negative beliefs about worry partially mediated the association between distress and worry</td>
</tr>
<tr>
<td>Ottaviani et al. (2014)</td>
<td>CR</td>
<td>IU</td>
<td>N1 = 31</td>
<td>Worriers showed hyper-activation into sympathetic and hypo-activation into parasympathetic during the worry condition compared to non-worriers. Worry is seen as a default/automatic and pathological response</td>
</tr>
<tr>
<td>Zlomke and Jeter (2014)</td>
<td>CR</td>
<td>IU</td>
<td>N = 1,092</td>
<td>IU partially moderated the relationship between daily stress and worry. Results showed also the contribution of IU in the development of anxiety disorders</td>
</tr>
<tr>
<td>Fergus and Wu (2013)</td>
<td>CR</td>
<td>IU</td>
<td>N1 (IU white population) = 1,185</td>
<td>Both groups, correlations between IU and worry are observed</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2 (IU black population) = 301</td>
<td></td>
</tr>
<tr>
<td>Norr et al. (2013)</td>
<td>CR</td>
<td>IU</td>
<td>N1 = 217</td>
<td>IU is seen as a transdiagnostic factor associated with anxiety symptoms and obsessive-compulsive symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>N2 = 241</td>
<td></td>
</tr>
<tr>
<td>Reuther et al. (2013)</td>
<td>CR</td>
<td>IU</td>
<td>N = 475</td>
<td>IU substantially mediates the relationship between perfectionism and the severity of distress</td>
</tr>
<tr>
<td>Dash and Davey (2012)</td>
<td>CR</td>
<td>IU</td>
<td>Not reported</td>
<td>High worry levels is linked with negative mood. Induced negative mood allowed the endorsement of cognitive appraisals known to increase systematic as opposed to heuristic information processing</td>
</tr>
<tr>
<td>Buhr and Dugas (2009)</td>
<td>CR</td>
<td>IU</td>
<td>/</td>
<td>Fear of anxiety symptoms are correlated with significant levels of worry</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>The combination of IU with fear anxiety lead to the highest level of worry (additive effect observed)</td>
</tr>
<tr>
<td>Davey et al. (2007)</td>
<td>CR</td>
<td>IU</td>
<td>Study 1</td>
<td>Study 1/Study 2: pathological worriers tended to be sensitive in negative mood and unresponsive in positive mood over the course of catastrophizing</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Study 2</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sample not reported</td>
<td></td>
</tr>
</tbody>
</table>

* | B/A response to uncertain threat aversion |
| Britton and Davey (2014) | CR | IU | Study 1 = 59 | Study 1, 2 & 3: Indirect effects of IU on inflated responsibility through negative mood are highlighted. Indirect effects of negative mood on IU through inflated responsibility are also revealed. Moreover, anxiety is seen as a motivational system implied to manage threat |
| | | | Study 2 = 63 | |
| | | | Study 3 = 61 | |
| Grupe and Nitschke (2011) | CR | IU | Not reported | IU is related with biased expectancies of aversion and heightened responses to aversion (anticipatory dysfunction) |
| Luhmann et al. (2011) | CR | IU | Not reported | IU is correlated with the tendency to select the immediately available, but less valuable and less probable rewards. Moreover, IU predicted decision-makers’ sensitivity to outcomes |
| Mahoney and McEvoy (2011) | CR | IU | N = 218 | IU is seen as a transdiagnostic factor, is associated with neuroticism and GAD symptoms but also leading to impairments in emotion regulation |
| Nelson and Shankman (2011) | CR | IU | N = 69 | IU is negatively correlated with startle during the uncertain threat condition in that those with higher IU had a smaller startle response. Perceived control over anxiety-related events partially mediated the relation between IU and startle to uncertain threat. IU is correlated with mitigated aversive responding to uncertain threat |
| Dugas et al. (2005) | CR | IU | Not reported | High levels of IU are significant correlated with ambiguous situation. Results observed more cognitive biases (impairments in information process) in participants with high levels of IU when they are confronted with ambiguous situations |

Notes: CR: cross-sectional design (quantitative study); IU: intolerance of uncertainty.
The second step in the study was to examine the cognitive state of IU. Sixteen results were retrieved (covering approximately 25% of the results for the review). The majority of studies investigated the link between IU and worry (10 of 16 studies). Studies demonstrated the intrinsic link where worry is seen as a mediator between the predictor (IU) and the issues (symptoms of anxiety, depression or OCD). Therefore, IU, worry and anxiety disorders are inseparable components. Researchers have demonstrated that excessive worries are related to positive beliefs about the function of worry (e.g. worrying help to avoid negative events and protect me against future threat), with poor or negative problem orientation, with cognitive avoidance of vivid mental imagery and IU. It seems that excessive and uncontrollable worry reinforced the vicious circle. Findings observed also that pathological worriers have a lower threshold for uncertainty and ambiguous situations but also tend to perceive more sources of threat in the environment compared to control. Lastly, certain results suggested that personality traits (mainly perfectionism) provoke more excessive worries and IU by the individual.

A last remark concerns more particularly the methodology of all eligible studies. In general, it exists a lack of consensus of the definition of IU. Through the data extraction and refinement procedures, others synonyms for IU are proposed (e.g. intolerance of ambiguity, need for predictability), which make scientific position difficult and do not allow generalization. Moreover, the high level of comorbidity between IU and anxiety disorders may have complicated the status of IU. It would be appropriate to systematically target the statistical status of IU (e.g. predictor, mediator …). Eligible studies were predominately quantitative. It would be useful to examine the IU through more qualitative design, allowing the understanding of certain interpersonal themes in anxiety disorders.

Nevertheless, the present clinical review of IU reveals potential areas of improvement in future research. It would be interesting to extend the range of the year of published studies, to increase the number of databases and to examine other variables such as health behaviours (obesity, drug addiction, alcoholism …); some personality’s factors (neuroticism, attachment or alexithymia) or to include this issue in the field of medical chronic disease (where the phenomenon of uncertainty is already activated).

6. Clinical implication
Few studies have investigated the cognitive process in IU across anxiety disorders. Some runways were cleared but it would be extremely interesting to measure (e.g. time reaction) the degree of the cognitive bias (attention and memory) by a computational task where intolerant of uncertainty individuals should activate some cognitive patterns (e.g. emotional Stroop, dot probe task …). Effective interventions will need to balance theoretically grounded models, careful clinical observations and empirical evidences. There are many opportunities for developing interventions across the spectrum of IU. It would be advantageous to include more “computational studies” in order to accurately understand the toxic pattern of thoughts (cognition) and psychopathological behaviours in IU across anxiety disorders.

Abbreviations
IU Intolerance of uncertainty.
GAD Generalized anxiety disorder.
MDD Major depressive disorder.
OCD Obsessive-compulsive disorder.
PD Panic Disorder.
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The authors declare no competing interests.

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http://dx.doi.org/10.1016/j.brat.2005.10.005
http://dx.doi.org/10.1016/j.janxdis.2010.06.015
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