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Gabapentin for the Treatment of Pain Manifestations in Children with Severe Neurological Impairment

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Abbreviations: Severe Neurological Impairment: SNI

Table of Contents Summary: This study reports on the efficacy of gabapentin and pregabalin for management of pain and distress in children with severe neurological impairment.

What is known on this subject: Pain, irritability and distress, often of uncertain origin, are significant issues affecting quality of life in children with SNI. Therapeutic options are limited but preliminary reports suggest the efficacy of gabapentin in these children.

What this paper adds: With the largest reported patient cohort to date, this study provides further evidence for gabapentin treatment in management of pain and distress symptoms in children with SNI. It also indicates that pregabalin may be effective as a second line agent.

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Contributors' Statement

Dr Collins conceptualized and designed the study, designed data collection instruments, collected the data, drafted the initial manuscript, and reviewed and revised the manuscript.
Dr Mannion designed the study, designed data collection instruments, collected the data and reviewed and revised the manuscript.
Dr Hussey and Dr Broderick conceptualized the study, designed data collection instruments and critically reviewed the manuscript for important intellectual content.
Prof Bourke and Dr Devins conceptualized and designed the study, designed data collection instruments, carried out the initial analysis and reviewed and revised the manuscript.
All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Introduction: Pain, irritability and feeding intolerance are common symptoms affecting quality of life in children with severe neurological impairment (SNI). There exist few therapeutic options for the many children in whom a specific organic etiology is not found. We performed a retrospective study to explore the use of gabapentin and pregabalin for symptom control in children with SNI.

Methods: This is a retrospective study involving patients currently attending the palliative care and gastroenterology departments of a tertiary level paediatric hospital in Ireland. Children with SNI on treatment with gabapentin for irritability, vomiting and pain of unknown origin were included. Information was gathered from medical and nursing documentation.

Results: A total of 42 patients were included. Irritability was reduced in 71% of patients. There was an overall symptom improvement in 76.3%, with increased gastrointestinal symptoms in only one patient. Pregabalin replaced gabapentin as a second line agent in 12 children. Some degree of benefit was reported in 9 children while 25% had substantial improvement. Adverse effects of both medications were rare.

Conclusions: Gabapentin and pregabalin have a role in management of symptoms of pain manifestations in children with SNI.

Introduction

Pain and distress symptoms are amongst the most challenging clinical problems faced by those caring children with severe neurological impairment (SNI). Up to 50% of children with cognitive impairment are reported to have pain episodes every week[1]. These are often frequent and persistent, with the most severely affected children having the most pain symptoms[2] . Assessing the severity and location of pain is difficult in this population due to difficulties with communication [3,4] and behavioral pain scales may be inaccurate due to physical impairment [3]. Parental assessment of pain has been shown to be accurate in these children[4–6] and many identify higher levels of pain in children with gastrostomy feeding and in those that suffer from gastrointestinal motility problems [1,4]. Symptoms are often associated with feeding and ascribed to the gastrointestinal tract[2].

Even in the context of an apparent gastrointestinal source, and despite extensive investigations, the underlying cause for pain and irritability often remains unclear [7]. Visceral hyperalgesia, an increased response and sensitivity to stimuli within the gastrointestinal tract [8], is a potential cause of this pain and irritability[9–11]. Children with SNI commonly have difficulties with constipation, gastroesophageal reflux disease and dysmotility[9]. This increases their risk of developing visceral hyperalgesia as damaged tissue, e.g. from surgery or inflammation, may lead to altered visceral afferent pathways[9,12].

Management of pain and irritability of unknown origin in SNI is difficult and options are limited[7]. In a study published over a decade ago, Hauer et al. first identified the potential of gabapentin in 9 children with SNI[9]. A follow up retrospective study by the same author identified an improvement in pain behaviors in over 90% of 22 children treated with gabapentin[13]. While gabapentin is licensed by the FDA for adjunctive treatment of partial seizures in paediatric patients over 3 years old [14] , there is anecdotal evidence that it is now

being used for pain manifestations in children with SNI[10] . We undertook this retrospective study of all patients with SNI treated with gabapentin for pain behaviors to see if we could replicate the findings of the seminal studies published by Hauer et al.[10,13].

Methods

This study is a retrospective chart review of paediatric patients with SNI attending the gastroenterology and palliative care services at Our Lady's Children's Hospital Dublin who had been prescribed gabapentin treatment. Severe neurological impairment was defined as non-verbal with gross motor function classification level IV- V. Patients needed to be on gabapentin for a minimum of 3 months to be eligible for inclusion. Patients on gabapentin treatment for confirmed neuropathic pain or with inflammatory bowel disease were excluded. Palliative care patients were identified using a chart review of all patients attending the palliative care service. Gastroenterology patients were identified by a word search for 'gabapentin' in the patient database. Patients who were treated with gabapentin for known organic diseases and those of normal cognition were excluded.

Information including demographics, investigations prior to commencing gabapentin, symptoms pre and post gabapentin, dosages, duration of treatment, efficacy and adverse effects were recorded. Where a decision to switch to pregabalin was taken, similar outcome data were recorded. For the purposes of the study the effectiveness of both gabapentin and pregabalin was interpreted from medical notes according to a predetermined 5 point scale; deterioration, none, minimal, good, very good. Patients were not involved in the design or the conduction of this research. Ethical approval was received by the research ethics committee of the hospital to undertake this study.

Results

There were 42 patients included in the study - 20 patients attending the palliative care service, 6 attending the gastroenterology service and 16 attending both (Table 1). The duration of follow up of patients on gabapentin ranged from 3 to 63 months with a mean of 21 months - a total of 75 patient years' follow up.

Prior to commencing gabapentin, investigations were undertaken based on clinical symptoms. 81% had imaging of the gastrointestinal tract., with esophagitis found in 3 patients. These patients remained symptomatic with irritability despite maximum anti-reflux medication. Other sources of irritability were excluded by dental reviews in 38% of children and orthopedic reviews in 62%.

Pain as a possible source of irritability was being treated a regular pain relief in 92.9% of children and 85.7% of children were on acid suppression treatment with either proton-pump inhibitors or H2 receptor antagonists prior to commencement of gabapentin.

Crying and irritability were the most frequently reported symptoms prior to commencement of treatment, occurring in 92.9% and 88% of children, respectively. Grimacing was present in 42.8%, as was vomiting. Dystonic movements were present in 38.1% of patients (Table 2).

The documented reason for commencing gabapentin in 62% of patients was irritability with a further 28.6% commenced for pain of unknown origin. The remainder were isolated cases commenced for feeding difficulties, dystonic movements and autonomic dysfunction.

A good or very good overall response to gabapentin was reported in 59.5% of patients, while minimal or no response occurred in 16.7% and 19%, respectively. Only one patient became more symptomatic with (increased vomiting) while taking gabapentin. Response was not documented in one patient. Improvement in irritability was reported in 71.4% of patients,

with 40.4% of patients requiring less pain medications. The duration of follow up of patients on gabapentin was 21 months (range 3 to 63 months).

Adverse effects were rare. There were isolated cases of increased vomiting, alopecia, raised amino transferase levels and increased 'twitching' which were attributed to gabapentin. Increased lethargy was reported in three cases (7.1%). There was an apparent loss of response over time in 4 children (9.5%). The duration of gabapentin treatment in these 4 patients ranged from 4 to 39 months with a mean of 25 months.

Dosing of gabapentin ranged from 5mg/kg once per day up to 30mg/kg three times per day. Most children were starting on 5mg/kg daily and increased to 20mg/kg three times per day, as required.

Gabapentin was switched to pregabalin as a second line agent in 12 of the 42 children, including two patients with lethargy, the patient with increased liver enzymes, six who had ongoing symptoms and three who felt the improvement from gabapentin had worn off. Treatment was discontinued in three further patients including the patient with alopecia, a patient who had no benefit and a patient who was no longer symptomatic (Table 3). Follow up of patients who changed to pregabalin ranged from 4 to 26 months with a mean of 13.5 months, constituting a total of 12 patient years.

Pregabalin was felt to have no effect in 2 patients (16.7%), minimal in 6 (50%) and good in 3 (25%). The efficacy was not documented in one patient. No patients reported either a very good response or a deterioration on pregabalin (Table 4). Only one of the 12 children (8.3%) suffered increased lethargy on pregabalin. There were no other documented adverse effects.

Discussion

The findings of this study support the use of gabapentin and pregabalin in the management of pain, distress and irritability in children with SNI. Over 50% of children achieved a substantial improvement of symptoms. Among those in whom there was an inadequate response, lack of medication tolerance or when efficacy was lost, pregabalin had some effect in a substantial majority.

With improvements in the medical management of complex conditions, increasing numbers of children with SNI are surviving through childhood. Pain behaviors are particularly troublesome in this group [15] and associated gastrointestinal manifestations are common. For example, in a study of 32 children with severe neurological impairment, Stallard et al. (2001) found 25 suffered pain every day, with 23 of those having moderate to severe pain[16]. In a study of 101 children Breau et al.[2] reported weekly pain in 35-52% of children with neurological impairment. Parents report higher pain frequency in those patients with a gastrostomy *in situ* or a history of gastrointestinal issues[4], and the gastrointestinal tract is the second most frequently identified origin of pain in children with severe neurological impairment by parents and carers [1,2].

In our experience, even in children with a suspected abdominal source for unexplained irritability and distress, a specific gastrointestinal cause for pain is not commonly identified. Visceral hyperalgesia is often invoked as the cause of pain and distress in this group of children [9,10] and the rationale for using gabapentin or pregabalin is strong given its likely role in reducing neuropathic pain[17] as well as its central effects [18]. Most children in this study were formally evaluated clinically by the paediatric gastroenterology service and investigated

where appropriate to exclude organic disease. Investigations and/or empiric treatment for potentially painful gastrointestinal conditions did not resolve the episodes. It is reasonable to assume that symptoms in such children likely arise from visceral hyperalgesia originating from either central and/or local gastrointestinal factors.

Despite being initially developed as an anti-epileptic medication, and used frequently in the treatment of neuropathic pain[17], there is increasing evidence for the use of gabapentin for symptoms of hyperalgesia[9,18,19], as we demonstrated in this study. The true mechanism of action of gabapentin is unknown. However, it is thought to have a predominantly central effect by binding to voltage gated calcium channels and inhibiting glutamate release.[19] Pregabalin is structurally related to gabapentin and has a similar inhibitory effect on voltage gated calcium channels [18].

With 42 patients included, this is the largest study of gabapentinoid use in the management of pain and irritability in children with SNI and its findings support previous research in the area. There exist only two previous published studies of gabapentin use in children with SNI both from Hauer et al.[10,13]. Our finding of improvement in 76% of children is slightly less than, but not dissimilar to, that reported in these two previous retrospective studies. In addition, we also noted a low rate of adverse effects, suggesting that this medication is safe and well tolerated in these children.

Loss of response to gabapentin in children with SNI has not previously been reported. We documented loss of effect in about 10% of children. Although the numbers are small, our data suggest that pregabalin might offer an effective alternative for these children and those intolerant of the medication.

This study has a number of limitations. It is a retrospective and therefore uncontrolled study relying on perceptions and interpretations of care givers and health workers, and therefore open to the biases in both groups. Despite this, documentation of response to gabapentin and pregabalin was present in all but one of both cohorts. Furthermore, it is accepted that parental reporting of pain symptoms in children with SNI is accurate[4,5], with good correlation between parental child and nursing ratings of pain in such children[6] .

Conclusion

This is the first study to corroborate the observations of Hauer et al. [10,13] and more than doubles the numbers of reported children with SNI receiving gabapentin. It suggests a possible role for pregabalin where gabapentin fails or is not tolerated. Perhaps more importantly it provides evidence for efficacy of these drugs in a very challenging and growing cohort of children where there otherwise exist extremely limited therapeutic options. There is now a compelling need for randomized controlled trial of gabapentinoid drugs in this group of vulnerable patients.

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Tables:

Table 1. Demographics

	n	**%**
Gender		
Male	23	54.8
Female	19	45.2
Age at referral		
0-5 years	26	61.9
6- 12 years	13	31
13- 18 years	3	7.1
Diagnosis		
Epileptic encephalopathies	7	16.7
Genetic	9	21.4
Cerebral palsy	16	28
Developmental delay - undiagnosed	10	23.8
Non verbal	41	97.6
Attending		
Gastroenterology	6	14.3
Palliative Care	20	47.6
Both	16	38.1

Table 2. Reported Symptoms

	n	%
Crying	39	92.9
Irritability	37	88
Dystonic movements	16	38.1
Grimacing	18	42.8
Regurgitation and vomiting	18	42.8

Table 3. Effectiveness of gabapentin

	n	%
Overall response to gabapentin		
Deteriorated	1	2.4
None	8	19
Minimal	7	16.7
Good	10	23.8
Very Good	15	35.7
Not Documented	1	2.4
Change in irritability		
Yes	30	71.4
No	11	26.2
Not documented	1	2.4
Pain reduction		
Yes	17	40.4
No	23	54.8
Not documented	2	4.8
Adverse effects		
None	31	73.9
Improvement reducing over time	4	9.5
Lethargy	3	7.1
Twitching	1	2.4
Alopecia	1	2.4
Vomiting	1	2.4
Elevated liver enzymes	1	2.4
Reason for change to pregabalin		
Lethargy	2	16.6
Ongoing symptoms	6	50
Elevated liver enzymes	1	8.3
Improvement reducing over time	3	25
Gabapentin discontinued	15	35.7
Of them		

Alopecia	1	6.7
Asymptomatic	1	6.7
No improvement	1	6.7
Changed to pregabalin	12	80

Table 4. Pregabalin

	n	**%**
Total switched to pregabalin	12	
Rationale for change to pregabalin		
Lethargy	2	16.6
Ongoing symptoms	6	50
Elevated liver enzymes	1	8.3
Improvement reducing over time	3	25
Efficacy of pregabalin		
Deteriorated	0	0
None	2	16.7
Minimal	6	50
Good	3	25
Very Good	0	0
Not Documented	1	8.4

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Abstract

Pain, irritability and feeding intolerance are common symptoms affecting quality of life in children with severe neurological impairment (SNI). We performed a retrospective study to explore the use of gabapentinoid medications for symptom control in children with SNI. Patients attending the palliative care or gastroenterology department being treated with gabapentin for irritability, vomiting or pain of unknown origin were included. Information was gathered retrospectively from medical documentation. Irritability was reduced in 30 of the 42 patients included. Pregabalin was used successfully as a second line agent in 9 children. These results support the use of gabapentinoids in this patient cohort.

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Main text

Pain and distress symptoms are amongst the most challenging clinical problems faced by those caring for children with severe neurological impairment (SNI). Up to 50% of children with cognitive impairment are reported to have pain episodes every week[1]. Even in the context of an apparent gastrointestinal source, the underlying cause for pain and irritability often remains unclear [2]. Visceral hyperalgesia, an increased response and sensitivity to stimuli within the gastrointestinal tract [3], is a potential cause of this pain and irritability[4].

In a study published over a decade ago, Hauer et al. first identified the potential benefits of gabapentin in 9 children with SNI[4] and a follow up study by the same author identified an improvement in pain behaviours in over 90% of 22 children treated with gabapentin[5]. We performed a retrospective study in 42 patients, the largest cohort studied to date, to see if the findings of Hauers' seminal studies[4,5] could be replicated, and to investigate if pregabalin is an appropriate second line agent for this indication.

A retrospective chart review of paediatric patients with SNI attending the gastroenterology and palliative care services at Our Lady's Children's Hospital Crumlin was performed. All patients who had been prescribed gabapentin treatment for pain or irritability of unknown origin were included. Information was gathered from medical notes. Prior to commencing gabapentin all children in this study were formally evaluated clinically by the paediatric gastroenterology or palliative care services, and investigated or treated empirically for organic disease, without improvement of their symptoms. The rationale for using gabapentin or pregabalin in these children with possible visceral hyperalgesia was based on its role in reducing neuropathic pain as well as its central effects[6].
Patients were not involved in the design or the conduction of this research. Ethical approval was received by the research ethics committee of the hospital.

There were 42 patients included in the study, with a duration of follow up ranging from 3 to 63 months and a mean duration of 21 months - a total of 75 patient years' follow up. The most frequently reported symptoms prior to commencement of gabapentin were crying and irritability, occurring in 39 and 37 children, respectively. A good or very good overall response to gabapentin was reported in 25 patients, while minimal or no response occurred in 8 and 7 patients, respectively. Improvement in irritability was reported in 30 patients and 17 patients required less pain medication (Table 1) Adverse effects were rare. Increased lethargy was reported in three cases and there were isolated cases of vomiting, alopecia, twitching and raised liver enzyme levels. There was an apparent loss of response over time in 4 children (Table 1).
Gabapentin was switched to pregabalin as a second line agent in 12 of the 42 children. There was no noted effect of pregabalin in 2 patients, minimal in 6, good in 3 and not documented in one (Table 2).

This is the first study to corroborate the observations of Hauer et al. [4,5] and more than doubles the numbers of reported children with SNI receiving gabapentin. It suggests a possible role for pregabalin where gabapentin fails or is not tolerated. Perhaps more importantly, it provides evidence for the efficacy of these medications in a very challenging and growing cohort of children where there otherwise exists extremely limited therapeutic options.

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Table 1. Effectiveness of gabapentin

	n	**%**
Overall response to gabapentin		
Deteriorated	1	2
None	8	19
Minimal	7	17
Good	10	24
Very Good	15	36
Not Documented	1	2
Change in irritability		
Yes	30	71
No	11	26
Not documented	1	2
Pain reduction		
Yes	17	40
No	23	55
Not documented	2	5
Adverse effects		
None	31	74
Improvement reducing over time	4	10
Lethargy	3	7
Twitching	1	2

Alopecia	1	2
Vomiting	1	2
Elevated liver enzymes	1	2
Reason for change to pregabalin		
Lethargy	2	17
Ongoing symptoms	6	50
Elevated liver enzymes	1	8
Improvement reducing over time	3	25
Gabapentin discontinued	15	36
Of them		
Alopecia	1	7
Asymptomatic	1	7
No improvement	1	7
Changed to pregabalin	12	80

Table 2. Pregabalin

	n	**%**
Total switched to pregabalin	12	
Rationale for change to pregabalin		
Lethargy	2	17
Ongoing symptoms	6	50
Elevated liver enzymes	1	8
Improvement reducing over time	3	25
Efficacy of pregabalin		
Deteriorated	0	0
None	2	17
Minimal	6	50
Good	3	25
Very Good	0	0
Not Documented	1	8

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Gabapentin for the Treatment of Pain Manifestations in Children with Severe Neurological Impairment- a Single Centre Retrospective Review

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Dr Collins conceptualised and designed the study, designed data collection instruments, collected the data, drafted the initial manuscript, and reviewed and revised the manuscript.
Dr Mannion designed the study, designed data collection instruments, collected the data and reviewed and revised the manuscript.
Dr Hussey and Dr Broderick conceptualised the study, designed data collection instruments and critically reviewed the manuscript for important intellectual content.
Prof Bourke and Dr Devins conceptualised and designed the study, designed data collection instruments, carried out the initial analysis and reviewed and revised the manuscript.
All authors agree to be accountable for all aspects of the work.

Abstract

Pain, irritability and feeding intolerance are common symptoms affecting quality of life in children with severe neurological impairment (SNI). We performed a retrospective study to explore the use of gabapentinoid medications for symptom control in children with SNI. Patients attending the palliative care or gastroenterology department being treated with gabapentin for irritability, vomiting or pain of unknown origin were included. Information was gathered retrospectively from medical documentation. Irritability was reduced in 30 of the 42 patients included. Gabapentin was discontinued in 15 children, 12 of whom then received pregabalin. Three children had a good response to pregabalin, six a minimal improvement and three no improvement. These results support the use of gabapentinoids in this patient cohort.

Main text

Pain and distress symptoms are amongst the most challenging clinical problems faced by those caring for children with severe neurological impairment (SNI). Up to 50% of children with severe cognitive impairment are reported to have pain episodes every week[1]. Even in the context of an apparent gastrointestinal source, the underlying cause for pain and irritability often remains unclear [2]. Both central neuropathic pain and visceral hyperalgesia, an increased response and sensitivity to stimuli within the gastrointestinal tract [3], are potential causes of this pain and irritability[4,5].

In a study published over a decade ago, Hauer et al. first identified the potential benefits of gabapentin in 9 children with SNI[4] and a follow up study by the same author identified an improvement in pain behaviours in over 90% of 22 children treated with gabapentin[5]. We performed a retrospective study in 42 patients, to see if the findings of Hauers' seminal studies[4,5] could be replicated, and to investigate if pregabalin is an appropriate second line agent for this indication.

A retrospective chart review of paediatric patients with SNI attending the gastroenterology and palliative care services at Our Lady's Children's Hospital Crumlin was performed. All patients who had been prescribed gabapentin treatment for pain or irritability of unknown origin were included. Information was gathered from medical notes. Prior to commencing gabapentin all children in this study were formally evaluated clinically by the paediatric gastroenterology or palliative care services, and investigated or treated empirically for organic disease, without improvement of their symptoms. The rationale for using gabapentin or pregabalin in these children with possible visceral hyperalgesia was based on its role in reducing neuropathic pain as well as its central effects[6].
Patients were not involved in the design or the conduction of this research. Ethical approval was received by the research ethics committee of the hospital.

There were 42 patients included in the study, with follow up ranging from 3 to 63 months and a mean duration of 21 months - a total of 75 patient years' follow up. The most frequently reported symptoms prior to commencement of gabapentin were crying and irritability, occurring in 39 and 37 children, respectively. A good or very good overall response to gabapentin was reported in 25 patients, while minimal or no response occurred in 8 and 7 patients, respectively. Improvement in irritability was reported in 30 patients and 17 patients required less pain medication (Table 1) Increased lethargy was reported in three cases and there were isolated cases of vomiting, alopecia, twitching and raised liver enzyme levels. There was an apparent loss of response over time in 4 children (Table 1). The mean duration of gabapentin treatment in those 4 children was 25 months. All were on the highest dose of 60mg/kg/day.
Gabapentin was switched to pregabalin as a second line agent in 12 of the 42 children. The dose of gabapentin was maximised prior to switching in 11 of the children. There was no noted effect of pregabalin in 2 patients, minimal in 6, good in 3 and not documented in one (Table 2). The mean duration of follow up of patients on pregabalin was 13.5 months.

Acknowledging the limitations surrounding the retrospective nature of this study, it nevertheless serves to corroborate the observations of Hauer et al. [4,5] and more than doubles the numbers of reported children with SNI receiving gabapentin. It suggests a possible role for pregabalin where gabapentin fails or is not tolerated. Perhaps more importantly, it

provides evidence for the efficacy of these medications in a very challenging and growing cohort of children where there otherwise exists extremely limited therapeutic options.

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Table 1. Effectiveness of gabapentin

	n	**%**
Overall response to gabapentin		
Deteriorated	1	2
None	8	19
Minimal	7	17
Good	10	24
Very Good	15	36
Not Documented	1	2
Change in irritability		
Yes	30	71
No	11	26
Not documented	1	2
Pain reduction		
Yes	17	40
No	23	55
Not documented	2	5
Adverse effects		
None	31	74
Improvement reducing over time	4	10

Lethargy	3	7
Twitching	1	2
Alopecia	1	2
Vomiting	1	2
Elevated liver enzymes	1	2
Gabapentin discontinued	15	36
Of them		
Alopecia	1	7
Asymptomatic	1	7
No improvement	1	7
Changed to pregabalin	12	80

Table 2. Pregabalin

	n	**%**
Total switched to pregabalin	12	
Rationale for change to pregabalin		
Lethargy	2	17
Ongoing symptoms	6	50
Elevated liver enzymes	1	8
Improvement reducing over time	3	25
Efficacy of pregabalin		
Deteriorated	0	0
None	2	17
Minimal	6	50
Good	3	25
Very Good	0	0
Not Documented	1	8