

# **EMICRANIA CRONICIZZATA**

**DIAGNOSI, TERAPIA, IMPLICAZIONI**

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# EMICRANIA: UNA DIAGNOSI E UN SINTOMO

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- Prevalenza: 1:1000
- Malattia neurobiologica e non psicosomatica
- Malattia neurovascolare
- Grosso impatto sociale (costi diretti e indiretti= assenza dal lavoro)
- Definizione secondo i criteri IHS

# CARATTERISTICHE, DEFINIZIONE E CRITERI DIAGNOSTICI

- Etiologia: centri di controllo dell'impulso nel bulbo cerebrale, poi diffusione a livello delle meninge (dura mater). Ruolo dei fattori scatenanti , anche psichici. Fattori genetici: ad es. Nella FHM sono coinvolti 3 geni. Ruolo dei neurotrasmettitori coinvolti.
- Prodromi
- Aura (“spreading depression”) nel 10-15% dei pazienti (visiva=scotomi), olfattiva, sensitiva)
- Attacco: durata da 4 a 72 ore, unilaterale o bilaterale, dolore pulsante, invalidizzante, accentuato dal movimento, accompagnato da nausea, ev vomito, fono-, foto-, osmofobia.



Fonte: [https://upload.wikimedia.org/wikipedia/commons/thumb/f/f5/Flickering\\_scotoma.png/800px-Flickering\\_scotoma.png](https://upload.wikimedia.org/wikipedia/commons/thumb/f/f5/Flickering_scotoma.png/800px-Flickering_scotoma.png)

- Specifica dell`attacco: con Triptani, dal 1990 (v.photo)
- Profilattica: con farmaci : quando farla e come farla e terapia adiuvante non farmacologica
- Importanza del diario del mal di testa

## Triptane in der Schweiz, Deutschland und Österreich

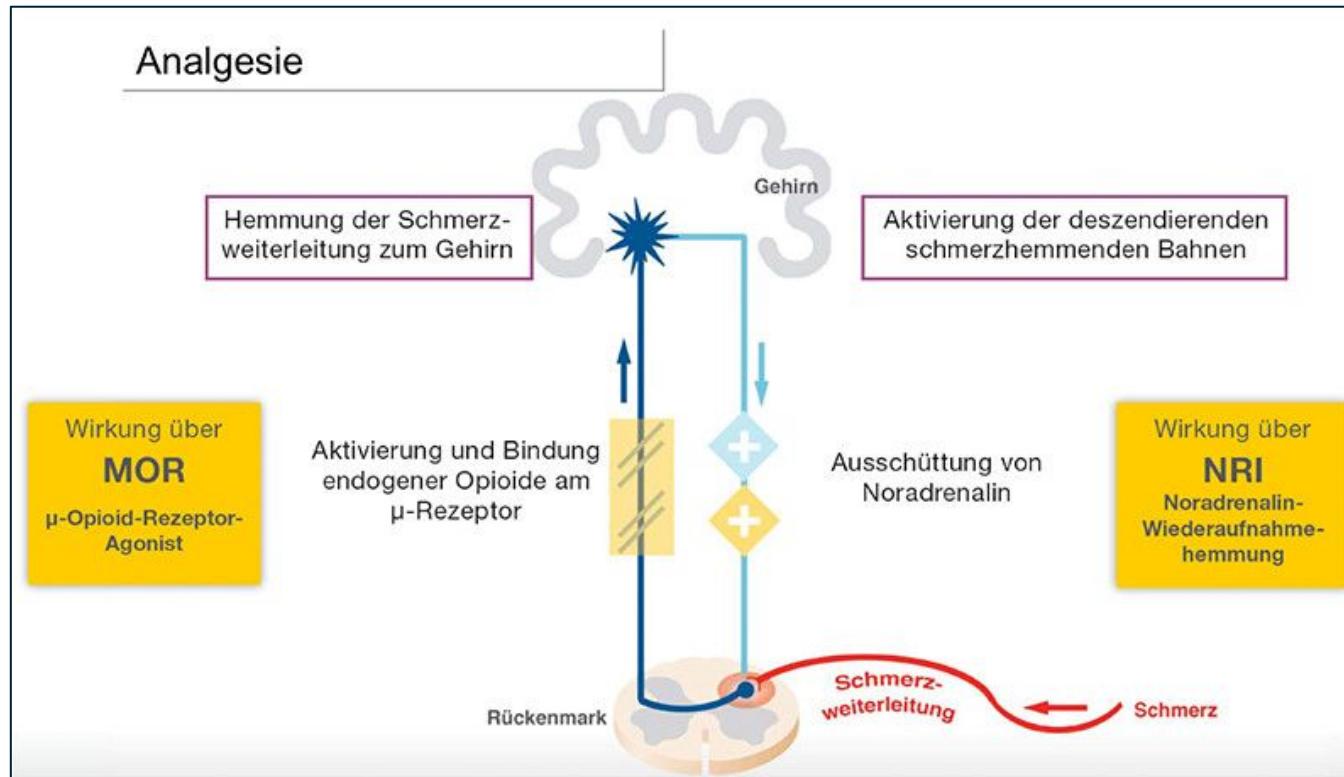
Sumatriptan (Imigran®)	Naratriptan (Naramig®)*	Zolmitriptan (Zomig®, Ascotop®)	Rizatriptan (Maxalt®)	Eletriptan (Relpax®)***	Almotriptan (Almogran®)**	Frovatriptan (Menamig®, Allegro®)
Tablette/T 50 mg	Tablette 2,5 mg	Tablette 2,5 mg	Tablette 5, 10 mg	Tablette 40, 80 mg	Tablette 12,5 mg	Tablette 2,5 mg
Zelrix**** 6 mg		Oro-Tablette 2,5 mg	Lingual-Tablette 5, 10 mg			
Nasalspray 10, 20 mg		Nasalspray 2,5, 5 mg				
Suppositorium 25 mg						
Injektion (Pen) 6 mg						

Tabelle 3: \* als OTC: Formigran®. \*\* als OTC: Dolormigran®. \*\*\* Relpax®: 80 mg nur in der Schweiz zugelassen. \*\*\*\* Zelrix®, nur USA.

# EMICRANIA CRONICIZZATA

- Se ne parla quando i giorni caratterizzati dall'emicrania sono più di 15 al mese per più di 3 mesi
- Esistono anche altre forme di cefalee cronicizzate (muscolotensiva, posttraumatica, Cluster, New onset daily headaches)
- Prevalenza internazionale: 2-5% della popolazione mondiale, 160.000 - 400.000 pazienti in Svizzera
- Concetto già descritto da Lipton a New York negli anni 90
- Nel 75% dei casi dovuta a abuso di **farmaci analgesici**, nel 25% causa poco chiara
- Grande impatto sociale

- Dolore sordo, pressione olocefalica ( colpisce tutta la testa), già appena alzati, costante, dura tutto il giorno, photofobia spesso presente, meno nausea, vomito e fonofobia
- Il paziente assume spesso farmaci durante le 24 ore
- Le caratteristiche tipiche dell'emicrania sono alterate
- La patofisiologia non è chiara , processi di sensitizzazione centrale a livello dei ricettori, disturbo delle vie discendenti del midollo spinale? v.foto
- Fattori importanti: comorbidità affettive, fattori genetici, adiposità, fattori lavorativi scatenanti



## La mia esperienza clinica, TERAPIA:

- Detossificazione dai farmaci implicati (di solito: Novalgina, Paracetamolo, Ibuprofene, Triptani a emivita corta), interruzione circolo vizioso
- TOSSINA ONABOTULINICA (BOTOX)
- Ev terapia cortisonica per 10 giorni
- Profilassi farmacologica in aggiunta al Botox, soprattutto se ci sono comorbidità
- Ev. Infiltrazione del Nervo occipitale (anche neuromodulazione occipitale)
- Miglioramento nell`80% dei casi ma ricadute del 40-50%



# TERAPIE AGGIUNTIVE IMPORTANTI

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- Concetto multimodale e multidisciplinare
- Terapia comportamentale
- Sport di “endurance”
- Intervenzione sui fattori psicosociali che mantengono il dolore, come pressione sul paziente da parte del datore di lavoro, scarsa autostima, problemi di coppia, ansia di prestazione, esigenza di essere in controllo di ogni situazione
- Terapia delle comorbidità, 25%-60% degli emicranici soffre di depressione e la depressione a sua volta è un fattore di rischio per l'emicrania e l'emicrania cronicizzata



A white cup of coffee with latte art sits on a saucer with a spoon, resting on a dark wooden surface. A small gold coin with a logo is visible on the right side of the table.

# PAUSA

Fonte: <https://pixabay.com/images/id-1958233/>

# ROLE OF KETAMIN IV AND METHADON P.O. IN CLUSTER HEADACHES

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- Cluster headaches have a low incidence and a male predominance. Although not life threatening, this disease, because of the intensity of the attacks, can result in tremendous pain, suffering and disability. Suicidality is not rare. The pathophysiology is still unclear, but it is known that the hypothalamus, the brainstem and genetic factors such as G1246A polymorphism play a role. We distinguish between episodic (EC) and chronic cluster (CC).
- In a controlled and monitored setting, we evaluated, between 6/2016 and 3/2019,
  - 47 patients, 34 males and 13 females with EC (69.6%) and CC (30.4%),
  - between the age of 21 and 72,
  - with 1-30 attacks /day.
  - We treated them with ketamine, an NMDA antagonist, iv, 0,5-0,75 mg/kg over 40-60 min, once/day for 3-11 times, in close intervals. All patients tolerated the infusion well.
  - 38.3% of the patients came to a complete stop of the attacks in less than 2 weeks and kept the result for at least 3 months (some, up to 3 years). In those patients who only partially responded, we added methadone po, another NMDA antagonist, in some cases up to a dose of 40 mg/day.

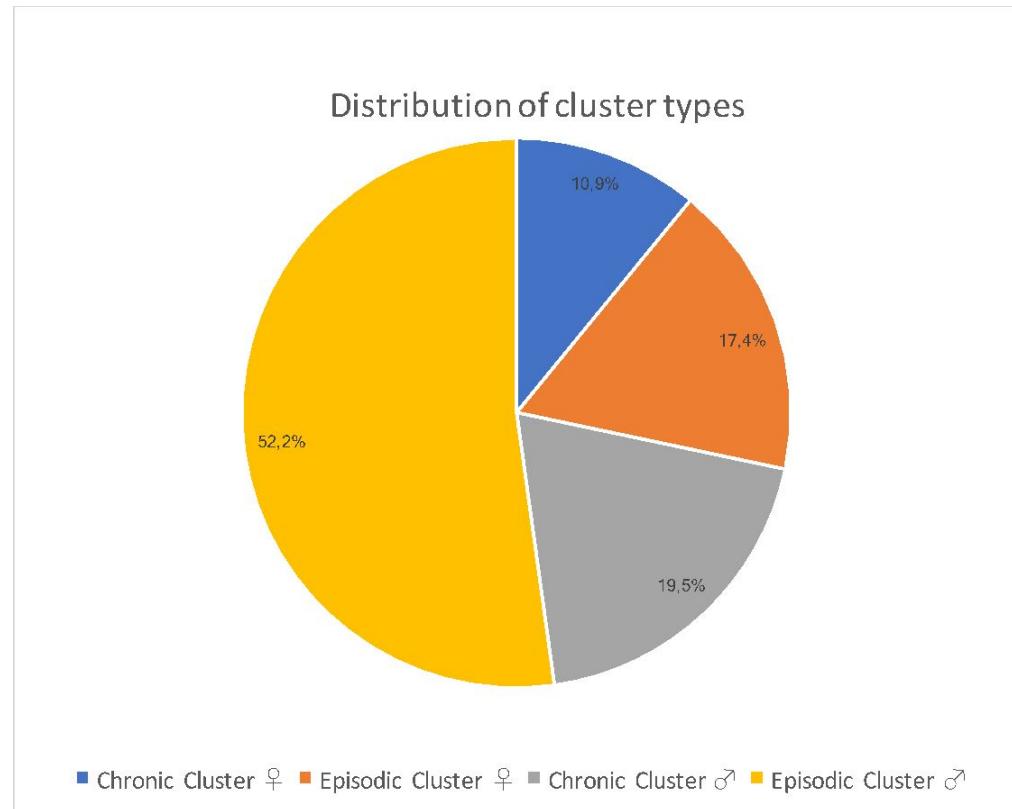
# ROLE OF KETAMIN IV AND METHADON P.O. IN CLUSTER HEADACHES

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- In 31,9% of patients we could abort the attacks in 2 weeks for at least 2 months.
- 19,1% were partial-responders (the attacks were milder and less frequent),
- 4,3% were nonresponders (mostly because they could not tolerate methadone) and
- 6,4% dropped out.
- Overall, 85% of the positive responses were in EC patients. Most patients had also been treated with pericranial Botox and ONI (occipital nerve infiltration) previously. We kept the baseline therapy if there was one (despite this therapy the patients had attacks, so it was irrelevant).
- We concluded that Ketamin iv alone and ketamine iv plus methadone po are useful therapies in aborting cluster headaches completely for a longer period of time, especially if, in patients with EC, treatment was initiated early in the cluster cycle. EC responded better than CC, which was to be expected. We postulated neuroplastic brain repair and neuroremodulation as possible mechanisms of action.

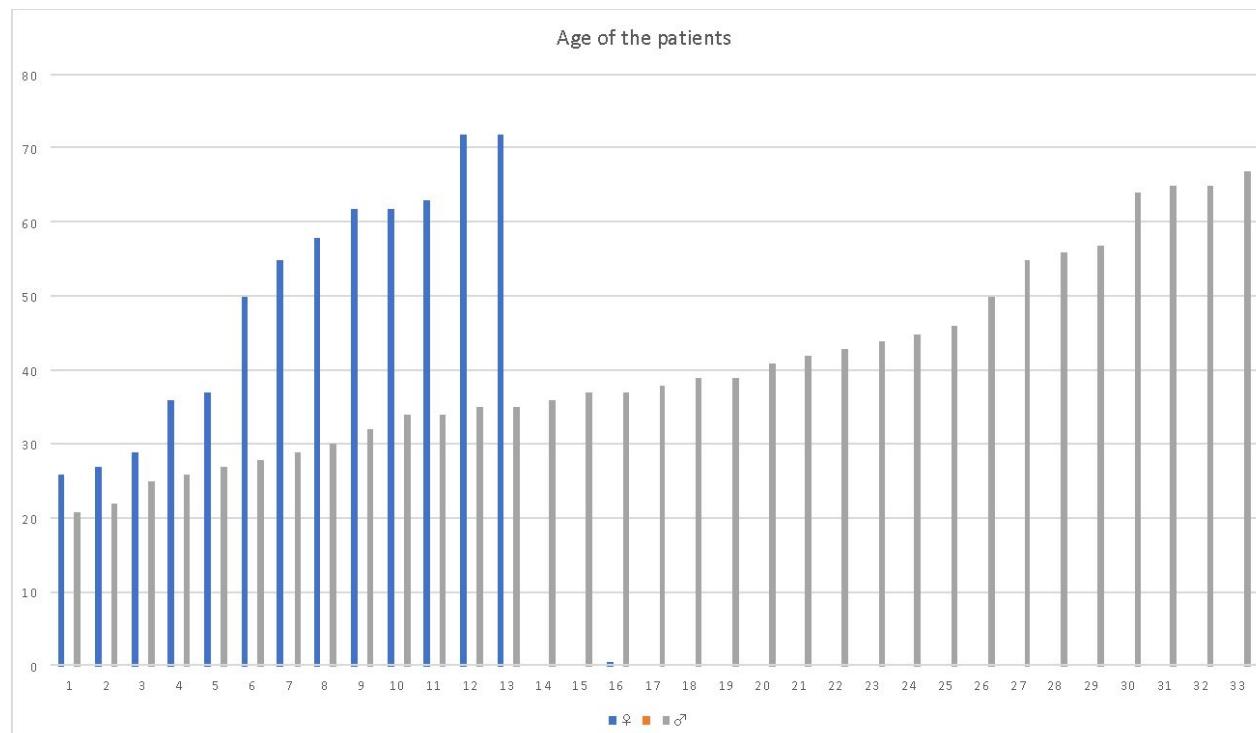
# TOTALS

- 47 patients
  - ♀: 13 □ 27.7%
  - ♂: 34 □ 72.3% (!)
- Chronic cluster: 30.4% (♂ 3 : ♀ 2)
- Episodic cluster: 69.6% (♂ 3 : ♀ 1)
- CC ♀: 10.9%
- CC ♂: 19.5%
- EC ♀: 17.4%
- EC ♂: 52.2%



# TOTALS

- Ø age: 43.3 years
  - ♀: 49.9 years
  - ♂: 40.7 years
- Min/max age
  - ♀: 26 – 72 years
  - ♂: 21 – 67 years
- Spread
  - ♀: 61%: 50+ years
  - ♂: 58%: 30-50 years



# WORKING STATUS

- At work: 73.3% ( $\text{♂}$  4.5 :  $\text{♀}$  1)
  - thereof EC 3 : CC 1
- Others: retired or not working

# ATTACK FREQUENCY

- Episodic:  $\square \emptyset$  2-3 attacks/day
- Chronic:  $\square \emptyset \pm 6$  attacks / day

- Nicotine
  - 65.9% are smoking nicotine ( $\text{♂}$  3.5 :  $\text{♀}$  1)
- Cannabis
  - 13.0% are consuming Cannabis ( $\text{♂}$  5 :  $\text{♀}$  1)

# FURTHER FINDINGS

- trigeminoautonomic disorders: 10.7% (♂ 2 : ♀ 3)
- hypnic headaches: 2.2%
  
- Ketamine not tolerated: 2.2%
- Methadone not tolerated: 8.7%
- noncompliant patients (with ketamin infusions close to each other): 6.5%
  
- also treated with Botox: 37.0%
- also treated with ONI: 39.1%
- also treated with ONI & Botox: 19.6%

# CALENDARIO A GRAPPOLO DA UN PAZIENTE

Episode beginnt wieder im Winter. Zuerst wieder Ankündigung mit einseitigem, leichtem Schmerz, Zahn, Auge, wie leichtes ziehen, 2,3 x, alle paar Tage. Dieses Jahr erstes Mal (bis jetzt) keine profilaktische Therapie, da letztes Mal Diabetes Typ 2 entstanden.

TAG	ZEIT	ATTACKE	MEDIK. AKUT	MEDIK. PROFIL
26.12.18	03:00	1x	Imigran-Spritze 1x	-----
27.12.18	02:00	2x	Imigran-Spritze 2x	-----
	09:00	3x( 2x)	Imigran-Spritze 3x	-----
28.12.18	02:00	4x	Imigran-Spritze 4x	-----
	08:00	5x (2x)	Imigran-Spritze 5x	----- Versuch: <b>Histamin-Arme Ernährung!</b> folgende Nacht
29.12.18	17:00	6x kurz	-----	----- keine Attacke!! am Morgen Spannungskopfweh
30.12.18	04:00	7x	Imigran-Spritze 6x	----- Spritze im Rechten Bein, wirkt nicht so schnell, Schmerz
31.12.18	01:00	8x	Imigran-Spritze 7x	----- bleibt ganzer Tag (nie mehr!!)
	14:30	9x	-----	-----
	18:30	10x (3x)	Imigran-Spritze 8x	----- (ev. wegen Ragout mit Fleisch und Tomaten???)
01.01.19	00:20	11x	Imigran-Spritze 9x	----- Neues Jahr fängt gut an :((((
	06:20	12x	Imigran-Spritze 10x	-----
	12:20	13x	-----	-----
	18:20	14x (4x)	-----	----- 1TL SKöl+ 300mg Vitamin B6 Abends, Nacht OK
02.01.19	06:30	15x	Imigran-Spritze 11x	----- 1TL SKöl +120mg Mag/1TL SKöl+300mg B6 Abends,OK
03.01.19	05:30 nur leicht	16x	-----	----- 1TL SKöl, Spannungskopfweh, Abends Ragout,Datteln
04.01.19	00.00 nur leicht	17x	-----	----- wieder eingeschlafen
	04:00	18x (2x)	Imigran-Spritze 12x	----- ganzer Tag gut, will kein SKöl und Vitamine nehmen
05.01.19	00:00 stark!!	19x	Imigran-Spritze 13x	-----
	05:20	20x	Imigran-Spritze 14x	-----
	12:30	21x	-----	----- nimmt ein Algifor. 14h isst Lachs!!
	15:00	22x	-----	-----
	18:00	23x (5x)	Imigran-Spritze 15x	----- 20:00h da Schmerz immer noch nicht weg ,2 TL SKöl
06.01.19	00:30	24x	-----	-----
	03:00	25x	-----	-----
	06:30	26x	Imigran-Spritze 16x	----- ganzer Nachmittag etwas Schmerzen
	13:00	27x	14h 2x Dafalgan	-----

# CALENDARIO A GRAPPOLO DA UN PAZIENTE

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	20:00 stark	28x	-----	-----	nimmt trotzdem nichts!
	22:40	29x (6x)	Imigran-Spritze 17x	-----	will ohne Schmerzen schlafen gehen!!
07.01.19	06:40	30x	Imigran-Spritze 18x	-----	
	12:00	31x	-----	-----	// ca. 01:30 zurück, geht schlafen
	20:00	32x (3x)	Sauerstoff (Triemli), ev anderes?	-----	mag nicht mehr, verzweifelt, geht ins Triemli !! kommt //
08.01.19	09:00	33x	-----	-----	kurze, schmerzhafte Attacke (ich an Arbeit), Nachmit. ok
09.01.19	00:30	34x	Imigran-Spritze 19x	-----	
	07:00	starke A. 35x	Zolnilg Nasenspray	-----	Medikament wirkt lange nicht!! Beruhig. erst nach 20 Min
10.01.19	23:00	36x (3x)	-----	-----	Dauer ca. 40 Min, isst Banane und Mandarine!!
	01:30	37x	Imigran-Spritze 20x	-----	
	15:00	38x	-----	-----	War unterwegs mit Auto !! //dann Nacht ok
11.01.19	23:30	39x (3x)	Imigran-Spritze 21x	-----	früh schlafen gegangen (21.30h), nach 90 min Attacke//
12.01.19	13:30	40x	-----	-----	War unterwegs mit Auto !! lange starke Attacke (2-3 Std.)
13.01.19	02:30	41x	Imigran-Spritze 22x	-----	Tagsüber endlich Attacken frei
14.01.19	07:00	42x	Imigran-Spritze 23x	-----	Nachts dauernd leichter Schmerz
15.01.19	05:45	43x	Imigran-Spritze 24x	1x KETAMIN 17h, Zürich, beim aufwachen leichter Schmerz	
16.01.19	03:00	44x	Imigran-Spritze 25x	-----	starke Attacke, 100'000 IE D3, Abends auch schmerzen
	00:00	45x	Imigran-Spritze 26x	-----	2 Std nach einschlafen
17.01.19	06:00	46x	Imigran-Spritze 27x	2x KETAMIN 14.30h Zürich, beim aufwachen Schmerzen, stärker	
	02:00	47x	-----	-----	ohne Spritze da mittelstark, Schmerz ausgehalten
				3x KETAMIN 14h St. Gallen, keine Schmerzen, alles gut	
18.01.19	-----	-----	-----	-----	Freitag alles gut, am Abend kurz Schmerz für 2-3 Min
19.01.19	-----	-----	-----	-----	Samstag gut, ausser 2x Nachts kurz Schmerzen 2-3 Min
20.01.19	02:00	48x	Imigran-Spritze 28x	-----	Attacke sehr stark
21.01.19	01:00	49x	Imigran-Spritze 29x	-----	
	07:00	50x	Imigran-Spritze 30x	4x KETAMIN 15h Zürich	
22.01.19	02:00	51x	-----	-----	mittlere Attacke, keine Imigran-Spritze
23.01.19	-----	-----	-----	5x KETAMIN 12h ZH, beginn Mittag Abend mit andere Medikamente:	
24.01.19	-----	-----	-----	ME,ON,TR,ESC Méthadone,Ondansetron, Trittico,Escitalopram	
25.01.19	02:00	52x	Imigran-Spritze 31x	ME,ON,TR,ESC	ME,ON,TR,ESCdauernd, diffus Kopfschmerzen, erschöpft, keine Attacke
26.01.19	-----	-----	-----	-----	dauernd, diffus Kopfschmerzen, erschöpft, keine Attacke
27.01.19	-----	-----	-----	-----	-am morgen etwas besser
28.01.19	-----	-----	-----	-----	

# SUCCESSFUL RESULTS

patients who responded in the **first 2 weeks** of infusion with a **stop of all attacks** and kept the result for **at least 3 months**

- Super responders (Ketamine only): **38.3%** (18/47)
- Full responders (Ketamine + Methadone): **31.9%** (15/47) } **70.2%** (33/47)
  - thereof EC 17/20 = 85.0% (!)
  - thereof CC 3/20 = 15.0%
  - thereof ♀ 3/13 = 23.1%
  - thereof ♂ 17/33 = 51.5%
- Partial responders: 19.1% (9/47)
- Non responders (Ketamine + Methadone): 4.3% (2/47)
- Patients stopped treatment: 6.4% (3/47)

# GRAZIE DELL'ATTENZIONE!

## Dr. med. Livia Granata

– Schmerzzentrum Granata –

FmH Neurology Specialist

SGSS Diploma in Pain Management

Diplomate, American Boards of Neurology  
and Pain Medicine



*„Conquering pain, improving lives“*