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Harnessing placebo effects by targeting expectancies

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SAMENVATTING *(DUTCH SUMMARY)*

Placebo-effecten zijn gezondheidsverbeteringen die optreden na toediening van een inactieve behandeling (i.e., placebo). Deze effecten worden doorgaans toegeschreven aan iemands verwachtingen over de heilzame werking van een placebo. Placebo-effecten zijn veelvuldig gevonden op pijn. Pijn kan ook beïnvloed worden door placebo-achtige effecten, dat wil zeggen, effecten die veroorzaakt worden door verwachtingen over een actieve behandeling of over de ervaring van pijn zelf. Ook andere lichamelijke klachten, zoals jeuk en vermoeidheid, kunnen beïnvloed worden door placebo- en placebo-achtige effecten, hoewel dit minder vaak onderzocht is. De behandeling van lichamelijke klachten kan mogelijk verbeterd worden door het benutten van deze effecten in de klinische praktijk. Om dat op een effectieve manier te doen is een beter begrip van placebo- en placebo-achtige effecten en van de rol van verwachtingen hierin van groot belang voor zowel onderzoekers als artsen.

Het primaire doel van het huidige proefschrift was om te onderzoeken hoe placebo-effecten benut kunnen worden om pijn en andere lichamelijke klachten te verlichten. Hiervoor richtten we ons op verwachtingen. We onderzochten verschillende manieren om verwachtingen te beïnvloeden (i.e., verwachtingsinducties: verbale suggestie, conditionering en mentale verbeelding) om de effectiviteit voor het verlichten van lichamelijke klachten, met name pijn, te bepalen. Daarnaast onderzochten we de rol van behandelkenmerken (i.e., de toedieningsvorm van medicijnen) en individuele kenmerken (bijv. persoonlijkheidskenmerken) in placebo- en placebo-achtige effecten.

In **Hoofdstuk 2** vatten we de theoretische en empirische literatuur over de invloed van verwachtingen op pijn samen. In de meest invloedrijke psychologische leertheorieën spelen verwachtingen een centrale rol. Er kan onderscheid gemaakt worden tussen drie soorten verwachtingen: stimulus verwachtingen (met betrekking tot externe stimuli en gebeurtenissen, zoals het ontvangen van een recept voor medicatie), responsverwachtingen (met betrekking tot interne, onvrijwillige ervaringen, zoals pijn) en verwachtingen over zelfeffectiviteit (*self-efficacy*, met betrekking tot het vermogen om gedrag uit voeren, zoals het ondernemen van lichamelijke activiteiten ondanks pijn). Van deze drie soorten verwachtingen worden responsverwachtingen over het algemeen gezien als het kernmechanisme van placebo- en placebo-achtige effecten. Ook wordt gedacht dat zij de grootste invloed op pijn hebben, gezien ze direct betrekking hebben op de ervaring zelf. Doorgaans worden drie leerprocessen van verwachtingen omschreven: leren via instructies (bijv. verbale suggestie), leren via conditionering

(directe ervaring van de samenhang tussen stimuli en/of gebeurtenissen) en observationeel leren. Daarnaast kunnen verwachtingen mogelijk ook geleerd worden door mentale verbeelding. We beschreven ook complexere verwachtingsconcepten (bijv. optimisme) waarin de samenhang van verwachtingen met gerelateerde emoties en gedachten gevat is. Met name optimisme en het catastroferen over pijn bleken geassocieerd te zijn met pijn, maar ook vertrouwen, piekeren en neuroticisme bleken invloedrijk, hoewel het onderzoek hiernaar beperkter is. Alles bij elkaar genomen onderstreept ons literatuuronderzoek de belangrijke invloed van verwachtingen op pijn en vergroot het ons begrip van de complexiteit van verwachtingen. Het beïnvloeden van verwachtingen via de verschillende leerprocessen lijkt een veelbelovende manier om placebo- en placebo-achtige effecten te benutten.

In **Hoofdstuk 3** bestudeerden we in een meta-analyse systematisch de beschikbare empirische literatuur om de grootte van de effecten van korte verwachtingsinducties op de pijn van patiënten te bepalen. We vonden dat verbale suggestie, conditionering en mentale verbeelding de pijn van patiënten kunnen verlichten. Er was vooral sterk bewijs dat verbale suggestie over de pijnstillende eigenschappen van een (placebo of actieve) behandeling placebo- en placebo-achtige effecten op de pijn van patiënten kunnen veroorzaken; een substantieel aantal studies vond effecten die gemiddeld statistisch matig tot groot waren. Slechts enkele studies onderzochten conditioneringsprocedures, welke altijd versterkt werden door verbale suggestie. Verrassend was dat de effecten daarvan niet groter bleken dan die van enkel verbale suggestie. Korte verbeeldingsoefeningen (bijv. gebruik makend van beelden van pijnvermindering door verdoving) hadden relatief kleine, hoewel veelbelovende, effecten op de pijn van patiënten. We bekeken tevens verschillende factoren die de effecten van de verwachtingsinducties mogelijk beïnvloedden. Opmerkelijk was dat de effecten van verbale suggestie op experimenteel opgewekte pijn en met name op acute procedurele pijn (bijv. pijn na een operatie) substantieel groter waren dan de effecten op chronische pijn (bijv. voortdurende zenuwpijn). Verder vonden we indicaties dat verbale suggestie effectiever was wanneer deze naar geïnjecteerde placebo's refereerde, dan wanneer deze naar orale of lokaal op de huid toegediende placebo's refereerde. Samenvattend suggereert onze meta-analyse dat de bevindingen van experimenteel onderzoek naar klinische situaties gegeneraliseerd kunnen worden in het geval van acute procedurele pijn, hoewel in mindere mate in het geval van chronische pijn. Verwachtingsinterventies, vooral verbale suggestie, zijn hiermee veelbelovende methoden voor het optimaliseren van reguliere pijnbehandelingen in de klinische praktijk, in ieder geval in acute gevallen.

In **Hoofdstuk 4** onderzochten we de effecten van zowel verbale suggestie als mentale verbeelding op pijn, jeuk en vermoeidheid als indicatoren van lichamelijke

gevoeligheid. In deze experimentele studie vertelden we een gezonde groep deelnemers dat een (placebo) capsule de gevoeligheid voor lichamelijke sensaties (zoals pijn, jeuk en vermoeidheid) kan verminderen. We vonden dat deze suggestie de verwachtingen van de deelnemers over de effecten van de capsule sterk beïnvloedde. Ook een nieuw ontwikkelde mentale verbeeldingsoefening waarin deelnemers zich hun best mogelijke gezondheid voorstelden, beïnvloedde de positieve en negatieve toekomstverwachtingen van de deelnemers. Echter, noch de verbale suggestie, noch de verbeeldingsoefening, noch de combinatie van beide beïnvloedde de lichamelijke gevoeligheid van de deelnemers, zoals bleek uit hun zelf-gerapporteerde en fysiologische reacties op experimenteel opgewekte pijn, jeuk en vermoeidheid. We vonden evenmin bewijs dat individuele verschillen, zoals de neiging van deelnemers om meer of minder optimistisch te zijn, hun reacties beïnvloedden. Deze bevindingen suggereren dat verwachtingseffecten niet altijd optreden. Mogelijk hangen ze, onder andere, af van de mate van specificiteit van de interventies, waarbij een focus op meerdere sensaties tegelijk of gezondheid in het algemeen minder effectief is dan een focus op een specifieke ervaring.

In **Hoofdstuk 5** onderzochten we of een nieuw ontwikkelde verbeeldingsoefening die specifiek gericht is op pijn placebo-achtige effecten kan opwekken. In de eerste van twee experimentele studies verbeeldden gezonde deelnemers zich dat ze minder pijn zouden ervaren tijdens een daaropvolgende pijnlijke koudwatertaak. Dit deden ze door zich een warme, waterdichte handschoen voor te stellen. De resultaten toonden dat de verbeelding van pijnvermindering (i.e., responsverbeelding) latere pijn kan verminderen. Belangrijk is dat deze effecten verklaard konden worden door de verwachtingen van de deelnemers over de latere pijn (i.e., responsverwachtingen). De effecten op pijn gingen echter niet gepaard met corresponderende fysiologische reacties (bijv. lagere hartslag). De tweede studie repliceerde deze bevindingen. In deze studie vonden we verder dat een aanvullende verbale suggestie over de effectiviteit van de verbeeldingsoefening de pijnstillende effecten niet of nauwelijks versterkte. Bovendien zagen we dat individuele kenmerken ook in deze studies de effecten niet voorspelden. Beide studies tonen dat placebo-achtige effecten op pijn opgewekt kunnen worden met responsverbeelding. Responsverbeelding lijkt daarmee een veelbelovende methode voor de behandeling van pijn, zelfs nog voordat de pijn daadwerkelijk optreedt.

In **Hoofdstuk 6** bekeken we verschillen in placebo-effecten van diverse toedieningsvormen van medicijnen (wat we ook in Hoofdstuk 3 zagen) door in een online vragenlijstonderzoek de onderliggende verwachtingen te meten. Een grote steekproef, representatief voor de Nederlandse bevolking, scoorde de verwachte

effectiviteit van zowel pijn- als jeuk-verlichtende medicijnen in verschillende toedieningsvormen: oraal, via injectie of lokaal op de huid. Overeenkomstig met onze eerdere bevindingen verwachtten respondenten dat injecties het meest effectief zouden zijn voor het verlichten van pijn. Voor het verlichten van jeuk daarentegen verwachtten respondenten dat lokaal toegediende medicijnen het meest effectief zouden zijn. Deze bevindingen geven aan dat de verwachte effectiviteit van medicijnen, en daarmee placebo- en placebo-achtige effecten, afhangen van zowel de toedieningsvorm als van de behandelde klacht. Aanvullende analyses toonden dat een hogere verwachte effectiviteit samenhing met verwachtingen dat de medicijnen langer aanhoudende effecten, een snellere werking, een grotere veiligheid en groter gebruiksgemak hebben. De verwachte effectiviteit was niet of slechts zwak geassocieerd met verwachte bijwerkingen, prijs en mate waarin de toedieningsvorm als beangstigend werd gezien. Ook individuele verschillen in demografische kenmerken, gezondheid, frequentie van medicijngebruik en persoonlijkheidskenmerken hingen niet of slechts zwak samen met de verwachte effectiviteit. Alles bij elkaar genomen suggereren deze bevindingen dat invasieve behandelingen niet per se krachtiger zijn dan minder invasieve behandelingen. In plaats daarvan spelen ook andere factoren een rol, zoals het soort klacht dat behandeld wordt en mogelijk ook de locatie van de klacht en de gangbaarheid van een specifieke toedieningsvorm voor de klacht.

Tot besluit onderstrepen de bevindingen van het onderzoek in dit proefschrift de invloed van verwachtingen op pijn en het potentieel van verwachtingsinterventies voor het verbeteren van de behandeling van pijn en andere lichamelijke klachten. We vonden dat placebo- en placebo-achtige effecten opgewekt kunnen worden via verbale suggestie, conditionering en mentale verbeelding. Vooral verbale suggestie lijkt de korte-termijneffecten van pijnbehandelingen te verbeteren bij patiënten. We vonden bovendien, voor het eerst, dat mentale verbeelding van verminderde pijn (i.e., responsverbeelding) pijnvermindering kan veroorzaken via de effecten op responsverwachtingen. Daarnaast zagen we dat verwachtingen over de effectiviteit van medicijnen ook afhangen van de toedieningsvorm en de behandelde klacht. Concluderend kunnen we stellen dat het benutten van placebo-effecten door ons te richten op verwachtingen veelbelovend is voor het verbeteren van de reguliere behandeling van lichamelijke klachten zoals pijn.

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CURRICULUM VITAE

Kaya Peerdeman was born on September 26, 1986 in Hoorn, the Netherlands. After obtaining her Gymnasium diploma at the OSG West-Friesland (with merit) in 2004, she completed her bachelor in Clinical Psychology at the University of Amsterdam (UvA) (with merit). In 2011, she completed the Research Master's programme in Psychology (major Clinical Psychology, minor Cognitive Neuropsychology; cum laude) and the master in Clinical Psychology at the UvA. Her main research project focused on the modes of thinking that determine the dysfunctionality of rumination. She obtained practical experience in psychodiagnostics and psychotherapy at the Universitair Psychiatrisch Centrum KU Leuven, campus Kortenberg, in Belgium. During her studies, she worked as a research assistant on various projects in Developmental Psychology and Religion Studies and organized lectures and an international conference on the Psychology of Religion for the psychology study association (VSPA).

She started her PhD research in 2011 at the Medical Psychology department of the Radboud university medical center in Nijmegen. In 2014, she moved with the whole research group to continue her work at the newly formed Health, Medical and Neuropsychology unit of Leiden University. Her research was funded by a NWO Vidi grant and later also an ERC consolidator grant awarded to prof. dr. Andrea Evers. During her PhD, in early 2015, she was a visiting scholar at Aarhus University in Denmark with prof. dr. Lene Vase. For her paper on the placebo-like analgesic effects of response imagery (Chapter 5), she received the EPP article award 2015/2016. During her PhD and as a lecturer at the department, she supervised a multitude of bachelor projects and master theses, taught workgroups, and gave several lectures. She was a member of the local and international organizing committee of the 1st official SIPS conference on Placebo Studies.

Currently, she is working as a post-doctoral researcher on prof. dr. Andrea Evers' Vici project to study the role of nocebo effects in the sensitization of somatic symptoms. In parallel, she continues her work as a lecturer.

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