# Colored Capsules – a Contribution to Drug Safety

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## Summary

**The unequivocal and precise identification of the drug product is the basis for compliance. Compliance is one of the critical factors with regard to drug safety and efficacy in any therapeutic area. Since elderly people have frequently to take more than one drug during a day, many differentiation options are necessary to achieve an unequivocal identification of the different drug products. Differentiation can either be achieved by color, by form or by imprint. Taken the very small size of drug products into consideration, neither the filigree imprint nor the variations in form are sufficient for the differentiation purposes.**

**Color perception which is part of the early visual system is an automatic process which can not be ignored and which remains to a certain but sufficient degree intact with age. Thus, colors can be recommended to aid elderly in medication management at least in a healthcare environment strategy which could consist of pharmacist intervention, simplified by the use of colors in conciliation, identification and application in various manner (e.g. colored dosage forms, colored patient information cards etc.). The possibility to combine different colors offers the possibility to create a broad range of different and among themselves discriminately combinations. Beside the differentiation aspect, colors can carry information and expectations that may support a therapeutic effect. Colors should therefore be considered and carefully selected during the pharmaceutical development of the final drug product.**

## Zusammenfassung

**Farbige Kapseln – ein Beitrag zur Arzneimittelsicherheit**

**Die eindeutige und unmißverständliche Erkennung von Arzneimitteln ist die Grundlage für Compliance. Compliance ist einer der kritischen Faktoren für die Arzneimittelsicherheit und den Therapieerfolg. Da gerade ältere Menschen häufig mehrere Arzneimittel am Tag einnehmen müssen, sind viele verschiedene Differenzierungsoptionen notwendig, um eine eindeutige Identifikation der Arzneimittel zu erreichen. Die Unterscheidbarkeit kann durch Farbe, Form und Aufdruck erreicht werden. Nimmt man die sehr geringe Größe von Arzneimitteln in Betracht, wird klar, daß weder die filigranen Aufdrucke noch die Formunterschiede eine ausreichende Unterscheidbarkeit schaffen.**

**Farbwahrnehmung als Teil des frühen visuellen Systems ist ein automatischer Prozeß, der nicht ignoriert werden kann und der über einen gewissen und ausreichenden Bereich auch mit dem Alter bestehen bleibt. Deshalb können Farben älteren Menschen die Bewältigung ihrer Medikamenteneinnahme in einem medizinischen Umfeld stark vereinfachen, etwa bei der Beratung durch den Apotheker, der Arzneimittelidentifikation und dem gezielten Einsatz (z. B. farbige Arzneimittel, farbige Patienteninformationen usw.). Durch die Möglichkeit verschiedene Farben zu kombinieren entsteht eine breite Palette von verschiedenen und unter sich voneinander unterscheidbaren Kombinationen. Neben dem Aspekt der Unterscheidbarkeit können Farben auch Informationen tragen, die den therapeutischen Effekt unterstützen. Die Verwendung von Farben sollte deshalb schon während der pharmazeutischen Entwicklung des Arzneimittels berücksichtigt werden.**

## Key words

- **Colored capsules**
- **Drug safety**

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## 1. Introduction

The population pyramid will shift dramatically during the next decade towards the older generation in Europe (Table 1). For drug safety and compliance it is inevitable to take a close look to the specific issue of this target group.

The pharmacokinetic and the pharmacodynamic behavior of drugs varies dependent from the age of the individual, especially the distribution of the drug, the metabolism (e.g. cytochrom-P-450 dependent processes) and the renal clearance [1]. Elderly people have generally a greater exposure to drugs based on the frequent administration of more than one drug for treatment of multiple and chronic diseases (polymedication) [2], which increases the risk for drug interactions. Studies have shown that about 25 to 50 % of the older patients did not follow the prescribed and intended medication regimen (non-compliance) [3–5], which is expected to be the reason for hospital admission in 6.0 to 11.4 % of hospitalization cases of elderly individuals [6, 7].

Beside the psychological factors for non-compliance [8] elderly individuals have additional physiological factors that lead to medication error or non-compliance (Table 2). Cognitive dysfunctions are commonly in the elder population. Gustavsson estimates that 10 % of people above 65 years of age develop dementia which is moderate to severe in 5 % [9]. The visual performance decreases physiologically with the age to an extent that only 50 % of the eyesight of an 80-year-old subject remains compared to the adolescent maximum [10]. Cataract, glaucoma, macular degeneration [11] and diabetic retinopathy [12] that occur numerously in this group of patients additionally deteriorates the visual performance, which directly impacts drug product identification or differentiation. Hearing may also be impaired leading to acoustic misunderstanding of therapeutic regimes [8].

To face the challenge of optimizing the compliance several interventions on medication management are required. From the cost point of view, keeping elderly people longer in their own houses will be less expensive to the society than either multiple hospital admissions or long-term residual care in other institutions [13].

The base for compliance is the understanding for the need of the therapy and the patient's commitment to follow the instructions properly. This requires the processing of complex information and their linkage to certain tasks over the entire time of therapy. Facilitating this process by supportive tools or dosage form design should already been addressed during drug product development. This article will try to provide the background and the rationale for using colorants in the dosage form design to facilitate the adherence to the therapeutic regimes and to improve the compliance.

**Table 1: Percentage of elderly people (65 and over and 75 and over) in the total population (World Population prospects of the UN).**

| | 1990 | 2000 | 2020 |
|---|---|---|---|
| Europe | | | |
| > 65 | 14.7 | 16.3 | 21.0 |
| > 75 | 6.6 | 7.2 | 9.9 |
| USA | | | |
| > 65 | 12.2 | 12.3 | 15.9 |
| > 75 | 5.0 | 5.8 | 6.5 |
| Japan | | | |
| > 65 | 12.0 | 17.2 | 28.1 |
| > 75 | 4.8 | 7.0 | 14.5 |
| World | | | |
| > 65 | 6.2 | 6.9 | 9.4 |
| > 75 | 2.2 | 2.4 | 3.4 |

**Table 2: Factors that influence compliance.**

| Psychological factors | Physiological factors |
|---|---|
| Trust in therapy | Cognitive dysfunction |
| Motivation | Visual dysfunction |
| Relationship with physician | Audio dysfunction |
| Judgment of therapy | |
| Anticipation of side effects | |

## 2. Human information processing

The development of human skills is a matter of gathering and processing a huge number of information. As our intellectual capacity is limited we will only select and process the most repeated and impressive information and keep it in our memory because we expect them to be important for our life.

### 2.1. Short and long-term memory

Memory can be described as a collection of nodes that become complex and increasingly inter-associated and interrelated through learning [14]. These nodes can be active or inactive and are termed short-term store or long-term store, respectively. Thus, information in the short-term store will be lost and gone when the active phase reverts to an inactive. Information in long-term store is said to be able to re-activate from an inactive into an active phase. This is due to the fact that long-term store is based on learned sequences of information processing which can be activated easily.

### 2.2. Controlled or automatic processing

If an appropriate signal is detected the information of the signal is processed by the human being. The processing can either be done in a controlled or automatic manner [14]. A controlled process is characterized by the temporary activation of nodes under the control of the individual. Controlled processing requires active attention of the subject by using short-term store which is limited at least in part by the capacity of short-term store. An automatic process is the activation of a special sequence of nodes that induce a well developed behavior without control or attention of the subject. Automatic processes do not require attention and they are not limited by short-term store capacity. Automatic processes can be developed by a certain degree of consistent training. An obvious example for an automatic process was described by Schneider and Shiffrin [14]. A red traffic light might initiate a breaking response when the perceiver is in a car, and a walking, halting or traffic scanning response when the perceiver is pedestrian.

### 2.3. Simultaneous processing

Frequently two tasks are carried out simultaneously. This may either be a between-task dual processing or a within-task dual processing. A between-task dual processing describes the performance of two unrelated tasks while a within-task dual processing is the performance of two unrelated tasks to accomplish a specific goal. A within-task dual processing is for example the identification of different medications and their right application. As demonstrated by several authors within-task dual processing can be improved and facilitated by practice [15].

Another study carried out by Schneider and Fisk investigated the possibility to carry out automatic and controlled visual search simultaneously and what are the corresponding resources required. They conclude that subjects can carry out an automatic and controlled process simultaneously without any measurable cost in sensitivity which was not the case when two controlled processes had to be performed simultaneously. Under consistent conditions, single and dual-task conditions improve significantly with practice leading to the assumption that extensive training support subjects to transfer dual task into automatic processing [16].

### 2.4. Visual detection

To induce an automatic or controlled process, detection of a stimulus or signal must take place. Visual detection of objects has been suggested to follow a two-stage process. In the first stage, which is called the pre-attentive mode, simple features are processed rapidly and in parallel over the entire field. The pre-attentive mode is limited to some primitive features or properties of objects like color, size, shape and brightness [17]. Features that can be detected in parallel in this stage are limited to color, orientation of line segments and certain shape parameter [18]. The pre-attentive stage performs basic analyses segmenting the visual field into functional units which can be selected for attention [19]. In the second stage, the attentive mode, attention is focused to particular locations or objects in the visual field [20].

### 2.5. Goal or stimulus-driven selection

Selection can be goal driven (top-down or endogenous) or stimulus driven (bottom-up or exogenous). Goal-directed is a voluntary selection when the subject controls what region or object will be visually processed to solve the current task. Stimulus-driven is related to the involuntary, task independent capture of attention [21]; it is supposed that selective visual attention is sub-served by two mechanisms called the saliency map and the selective mapping field [22]. The saliency map is the assessment of the overall conspicuity of a location which combined the information of the individual map into a total measure of conspicuity. This saliency map is part of the early visual system, which encodes simple properties, e.g. colors. Since the computation of color requires the entire visual field as has been demonstrated psychophysically [23, 24], it is supposed that computation of colors is prior to the selection and further processing. The selective mapping is described as the selection of the most conspicuous location, whereby only one location can be selected at the same time [22].

## 3. Color perception

According to the postulated opponent color theory of Hearing in 1878, which is accepted in the natural sciences as a basic model for color vision [25], color perception is based on the elementary colors, the achromatic colors white and black and the chromatic colors red, blue, yellow and green. The colors are elementary because they do not have any resemblance to each other. The elementary "pure" colors are carried by each human as the natural reference color. The color perception is a process of comparing a seen color in resemblance with the elementary colors.

Colors carry associated meanings and symbolic values. The color perception in terms of meaning is a highly complex and multidimensional process which is dependent from several components and varies with the context. A cultural context was described by Adams and Osgood to influence the color meaning. For example, for the Mexican population blue is associated with a strong potency which can be explained by the fact that blue has a religious association with the Virgin Mary and Heaven and that the uniforms of the policemen are blue as well as the fifty-peso bill. Adams and Osgood also assume that the actual environmental situation may influence the evaluation of colors as, for instance, the positive evaluation of yellow by the French population when the test was carried out in the dark month of February while subjects may have been thinking of sunshine [26]. Differences in color perception and meaning occurred when laymen and color specialist (e.g. architectural students) were compared [27]. As colors are part of the environment, Sivik investigated color denotation and connotation of the isolated color and their exterior context. He came to the conclusion that evaluative variables of meaning of color were most sensitive to contextual changes like coloration of buildings than other connotative dimensions like warm-cold


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and hilarious-serious evaluation [28]. In addition to the influence of color perception in the context of an object or a form, we have to take into account that colors generally do not appear in an isolated form and therefore must be seen in the context of one or more other colors [29]. Bergström found the importance of illumination as a factor of color perception. According to this work the visual system compares the reflecting light at the boarder lines to get information about illumination, color and three-dimensional form of the object [30]. The context of related color and illumination together on the colorfulness of a color was emphasized by Hunt recently. He describes that the colorfulness of a color is being affected greatly by the background and the reflectance factor of the background [31].

In the context of pharmaceutical drug products the perception of colors has been investigated by Hersberger [32]. The study could demonstrate that certain colors have a clear perceived effect in a specific disease, others are unanimously judged. The perceived effects on the motor function were stimulating for yellow, red and light blue, while brown and purple were perceived as inhibiting. For the expected effect on the heart rate, white pink and brown were perceived as calming while red was stimulating. White, yellow and light blue had a relaxing effect on the respiratory function which was perceived as tightening for dark blue and brown.

A practical confirmation of the perception of colors and its link to the therapeutic effect is the study of Huskisson [48]. He investigated the analgesic effect of different colored placebo capsules and found that red, followed by blue, had the highest pain relief score, while the effect of green and yellow were only minor (Fig. 1).

## 4. Color detection and processing

As described above, color perception is part of the early visual system. According to general child psychology, the attention to and interest in color stimuli is prominent even in very young children [27]. Moreover, the color names are learned at this very early age and are supposed to be over-learned over the years [33]. Thus, it is not surprising that colors can not be ignored by human being. Chaparro et al. could demonstrate that the best detected color stimulus was seen 5-6 fold better than the best luminance spot [34]. In addition to this a color singleton was shown to capture attention involuntarily even when the subject had attentional set for an abrupt onset singleton, supporting the finding that color perception is an involuntary automatic process that do not require attention [35]. With the visual (color) detection which takes place in the pre-attentive mode [36] the information is transferred to an automatic processing. In case of repetition of the color stimulus, the stimulus facilitates the automatic processing in form of an automatic reaction, the so called "priming effect" [37]. The priming effect is a cognitive function which remains stable with age [38].

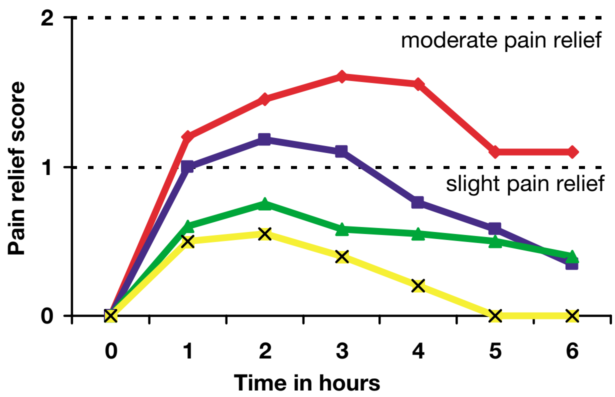


**Fig. 1: Pain relief scores for single doses of placebo capsules in four different colors.**

The influence of age, depression and dementia on color perception was studied using the Weigl performance test [39]. The Weigl performance test [40] is a sorting test of different colored forms according to the competing categories of form or color. Color perception was shown to be less affected in age, depressed and demented subjects compared to the perception of the form. The results are summarized in Table 3.

Alzheimer Disease is suspected to be responsible for 50 % of the dementia cases. Alzheimer Disease patients suffer from a poor short-term memory. Thus, the over-learning of colors in the early childhood was expected to be little affected by Alzheimer Disease and should remain a useful stimulus to aid memory. Regarding color naming, color discrimination and color preference no significant difference was seen between patients with Alzheimer Disease and non-demented subjects [41]. The authors conclude that colors should be used in the healthcare environment for geriatric wards.

Also normal geriatric patients can benefit substantially from the use of color-coded schemes in terms of compliance. Using color-coded pill bottles combined with color-coded weekly pill trays the deviation from the ideal pill count could be reduced from 17.1 to 1.7 % [42].

In a recent study Hersberger investigated the color detection in elderly. The objective of this study was to find out the most suitable colors or color combinations of hard gelatin capsules for geriatric patients in terms of

**Table 3: Mean corrected sorting times (s) (mean ± SD; n = 24) [39].**

| | Irrelevant dimension constant | | Irrelevant dimension varies | |
|---|---|---|---|---|
| | Color | Form | Color | Form |
| Demented | 10.53±6.37 | 15.13±5.38 | 14.45±5.53 | 20.87±6.22 |
| Depressed | 8.52±3.59 | 9.47±4.07 | 9.24±3.31 | 10.87±3.79 |
| Normal old | 9.31±4.91 | 11.18±5.04 | 9.53±5.19 | 12.89±5.18 |
| Normal young | 2.23±0.64 | 2.17±0.64 | 2.39±0.65 | 2.47±0.76 |

identification, discrimination and preference [32]. The results suggest that white and, to some extent, yellow combined with saturated colors like light blue, red, green, dark blue and orange are the most suitable colors for combination, while dark colors like brown and violet combined with dark colors can not be recommended as suitable color combinations. It is evident to mention that the most suitable colors for combinations considered by this study are the elementary colors which are, according to the opponent color theory, the natural reference colors. It can be supposed that even in impaired vision the visual performance of the elementary colors should be influenced less than "mixed" colors which have to be processed for resemblance.

## 5. Use of colorants for pharmaceutical dosage forms

When developing a new pharmaceutical product colors can be applied in various forms for the finished product. Colors are used already widely for the Logo and on the carton and blisters of each product to provide product information and create a brand image. However, once the product is prepared for the administration, it is separated out of the box and blister and tends to loose his connection with the primary packaging.

To maintain the identification and enable the patients to "automatically process" the right administration of the product, the dosage form as such should carry the information itself. Fig. 2 shows differently colored two-piece capsules and white tablets as elderly patients on polymedication will receive the medication from the nurse or after own preparation for the day.

It is obvious that the colored two-piece capsules remain easy detectable and distinguishable, while the white tablets only vary in dimension, which is hard to distinguish or to relate to any therapy. Imprints can further help in distinguishing when the imprint color is in contrast to the capsule color. Doctors or pharmacists can actively use these color differences for advice and patient education to improve the compliance. For example: "The blue and white capsule is against your dizziness, take the blue and white in the morning. The yellow and green helps you to sleep better, take the yellow and green with your evening meal."

The main questions that should be answered before considering a color or color combination are the following:

1. What is the therapeutic class of the drug and which effects are expected?
2. What is the targeted patient population?
3. What other medications already exist in the therapeutic class, with which products this medication will be combined?
4. Will the product be marketed in different dose strength?

**Fig. 2: Example for polymedication seen from different distances.**

*What is the therapeutic class of the drug and which effects are expected?*
Several studies [26, 43, 47–49] have confirmed that colors are associated with certain expectations or perceptions when used for pharmaceutical products. Fig. 3 shows an example for the likely treatment effect on mood of the main colors used in pharmaceutical dosage forms. A mainly stimulating effect is recognized for red, yellow and light blue, while dark blue, brown and pink are perceived as calming.

It is obvious that a pharmaceutical product for sleeping disorders should not be of a red or yellow but of a calming color like dark blue or brown.

*What is the targeted patient population?*
With increasing age the visual performance declines and makes it more difficult to distinguish certain color combinations. The "mixed" colors, like purple, brown and pink become difficult to identify especially when mixed with each other. From the studies done by Hersberger [32] it appears that white and, to some extent, also yellow combined with colors such as light blue, red, green, dark blue and orange are the most suitable color combinations that can be distinguished and identified easily by elderly patients.

*What other medications already exist in the therapeutic class, with which products this medication will be combined?*
The long use of a specific color for a therapeutic class of compounds can already create a certain perception of the effect. New products should be sufficiently different but not in total contrast to the existing therapy. If a certain product is often combined with another drug product, special attention should be drawn to the reference product to allow easy differentiation of both products in combination. The individual colors or color combination of each drug product can then be used to guide the patient by the color or color combination and the mode of administration (automatic processing).

It must be noticed that a straight forward color or color combination of a drug product for identification and compliance reason can directly be linked to the creation of a brand image to create a competitive marketing advantage as well. The "purple pill" is just one example of a strong brand image created by a color combined with an imprint (Fig. 4).



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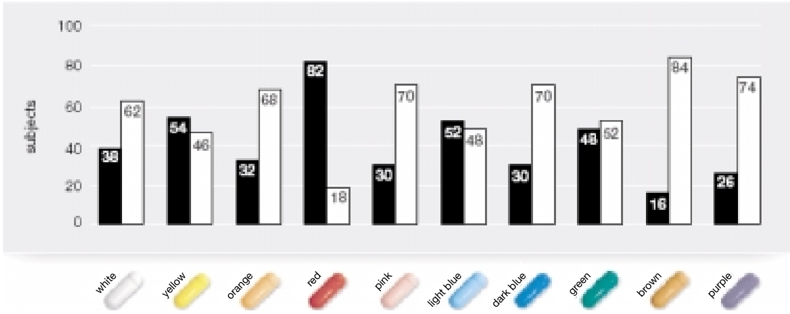


**Fig. 3: Perceived effect on the mood by elderly patients. □ calming; ■ stimulating.**

*Will the product be marketed in different dose strength?*

Several products are marketed in different dose strength to allow individual dosing. Especially with low-dose products, the size difference of the tablet or capsule is minor or not existing and medication errors are most likely to occur, by elderly patients as well as by the nurses preparing the individual treatment of the patients. For such products color combinations to clearly differentiate the different dose strength of the same product should be applied. For example, the ACE inhibitor ramipril is on the market in 4 different dose strength, a 1.25, 2.5, 5.0 and 10.0 mg capsule. While the body of the capsule remains white, the color of the cap is of increasing shade from yellow, orange, scarlet to blue for the highest strength. Rivastigmin is another example, where mono-chromatic colors of increasing shades are used for the doses 1.5 mg (yellow), 3.0 mg (orange) and 4.5 mg (red) and a bi-chromatic color for the highest strength of 6.0 mg (orange/red).

## 6. Discussion

Elderly people are known to have difficulties with independent drug management, especially in case of polymedication with complex administration schemes. As drug management starts with the physician's prescription, then passes the pharmacist and remains for up to three month or even longer in the sole responsibility of the elderly patient, various interventions are requested to maintain the compliance. Several suggestions were made and summarized by Tett [13].

Medication management is a repetition of a sequence of tasks. The sequence of tasks consists of the identification of the drug product, the application mode and time and the application itself. In the beginning, medication management is a controlled process and requires active attention. Controlled processes are capacity limited, especially for long-term medication management in elderly it is desirable that medication management becomes, to a certain extent, an automatic process. Automatic processing is described as a set of learned sequences of information [14]. Learned processes can be assumed not to be limited to single tasks, as demonstrated by Schneider et al. who found that single and dual-task performance improved significantly with training [16], which was confirmed by the within-dual task processing investigations by LaBerge et al. and Welford [15, 44]. Thus, one can assume that medication management can become an automatic process which would facilitate long-term medication management in terms of compliance.

One important part of the sequence of action is the identification of the drug which should be easy and clear because any doubt may create insecurity that will lead to an increased rate of errors. Visual performance was described to be a two-stage process. In the first stage, the pre-attentive mode, a basic analyze is performed to divide the visual field into functional perceptual units and a spatial unit is selected for evaluation. The evaluation is then done in a second stage, the attentive phase [36]. Koch and Ullman describe a slight different mechanism for attention which is closer to the cortical psychology and anatomy. [22]. They proposed the existence of an early conspicuity within a particular feature dimension (e.g. color). The saliency map, which is still part of the early visual system, combines the information of the feature maps into one unique measure of conspicuity. The selective mapping then transfers the most conspicuous location into a more central one. However, both theories are in accordance with the computation of color before selection. One can assume that, due to color computation before selection, color can influence the selection process.

As the eyesight decreases significantly with age and can be additionally impaired by pathological changes, the perception of color may not be different in elderly compared to young subjects. The investigations of Grewal et al. demonstrate that the sorting time of the color dimension using the elementary colors, red, blue, green and yellow was longer in normal aged (mean age 74 years), depressed (mean age 75 years) and demented (mean age 75.3 years) persons. Within the three age groups the sorting times were not markedly different, even if the irrelevant dimension (form) varies, except

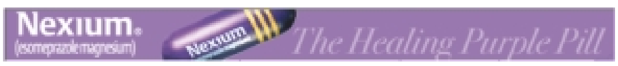


**Fig. 4: The "purple pill" (www.purplepill.com).**

for the demented patients who needed longer for sorting in case the irrelevant dimension varies. However, the sorting time for the dimension color was significantly shorter for the three groups of elderly than for the dimension form for both, constant and varying irrelevant dimension, which was not the case in normal young subjects [39]. This suggests that the color identification (sorting time) is prolonged in elderly but that the color perception remains a stable function.

Color perception in elderly was investigated by Hersberger and Wijk et al. in form of color naming experiments. Under good light condition on a white surface elderly showed a very good performance in color naming of the elementary colors but also pink and orange (less than 6 % mistakes). Unfortunately, this study did not include a young control group [32]. Similar results were reported from Wijk and Sivik in elderly and demented patients who found 10.7 and 9.8 %, respectively, of mistakes in color naming over the whole range of colors presented including the complex colors, turquoise, brown, purple (violet) which were also reported by Hersberger to be difficult to identify, e.g. brown with 26 %, purple with 18 % of mistakes [41]. In another study Hersberger investigated the discrimination of color combinations in elderly. She came to the conclusion that the most suitable color combination must have a good contrast and consists of a saturated or dark color combined with a bright color like white or yellow. When splitting the color combination into a single color the most frequently selected colors in terms of suitability were the elementary colors red, white, blue, yellow and green. This is in full accordance with the previously mentioned results that the perception, especially of the elementary colors, is stable with age and even under demented conditions.

The selection according to Yantis' work can be a voluntary goal directed selection or an involuntary stimulus driven selection [21]. It was found by Theeuwes that color singleton can capture attention involuntarily, even so the subject has an attentional set for an abrupt onset singleton [35]. This would support the theory that a color singleton is strong enough to interfere with a goal directed selection. However, further studies could not proof the findings of Theeuwes [21, 45, 46], which is in correspondence with the theory that selection is based on the degree of conspicuity [22]. With regard to the fact that colors are learned in a very early age so that they are in long-term store and even over-learned and that they are perceived before the selection process, we can expect that their degree of conspicuity is very high. The findings of Chaparro et al. that color stimuli are seen 5–9 fold better than luminance spots support this expectation [34].

A color stimulus can induce an automatic execution of a sequence of actions. This automatic processing does not require attention and can even be carried out simultaneously to a task that requires active attention. It has been demonstrated by several authors that automatic processes can be developed to a certain degree by consistent training. Guided by a pharmacist or a nurse during the initial phase of a new therapeutic scheme a patient can learn to process the color of a drug product to a scheme of administration quickly into an automatic processing facilitating his therapy and improving his compliance.

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